Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(4): 79
http://doi.org/10.31083/j.ceog4904079

Review

Foetal pain and anaesthesia during prenatal surgery

Carlo V Bellieni[1,*]

[1]Pediatric Department, University of Siena Viale M Bracci 36, 53100 Siena, Italy
*Correspondence: bellieni@unisi.it (Carlo V Bellieni)
Academic Editor: Kazushi Watanabe
Submitted: 6 December 2021 Revised: 16 January 2022 Accepted: 23 January 2022 Published: 30 March 2022

Abstract

Objectives: Foetal surgery is a relatively new branch of medicine; the health providers involved are currently wondering what kind of anaesthesia should be provided to the foetuses. In the last few years, new advances have been reported on foetal sensoriality and capability for feeling pain; meanwhile alerts have been issued on the risks of prolonged anaesthesia in the early infancy. Aim of this paper is reviewing the main data on foetal pain, to be aware of which is the time in pregnancy when it is likely to be felt. The secondary aim is to point out which are the anaesthetics and analgesics appropriate for prenatal surgery. **Mechanism**: A review of the literature published in the last 20 years in the field of fetal sensoriality and fetal sergery has been carried out; the most pertinent papers have been retrieved, and their conclusions are here summarized and analysed. **Findings in brief**: Pain can be felt by the human fetus in the second half of pregnancy: data of physiological and behavioural studies show it with increasing evidence, as long as the gestational age increases. With regard to the best anaesthesia in this case, it seems that the mere anaesthetics given to the mother, though apparently sufficient during laparoscopic surgery, are not sufficient to anesthetize the foetus during open surgery; here some references are given for the best and safest foetal direct analgesic treatment. **Conclusions**: Surgeons should approach carefully fetal surgery, according with the latest findings in this field.

Keywords: pain; foetus; surgery; pregnancy

1. Introduction

Foetal pain is a problem usually dealt with for its ethical implications; but it is also a problem for the surgeons, who are increasingly asked to perform challenging interventions on the foetus before birth. As this type of surgery has become today quite widespread, it is mandatory having certainty about the type of anaesthetic to be administered to the mother or foetus: this now has become a necessary topic in the modern approach to pain [1,2]. Aim of this review is to report the state of the art about foetal pain, the opportunity about using anaesthetics in these interventions, and the type of analgesia to be used during prenatal foetal interventions.

2. Pain pathways development

For a potentially painful stimulus to generate pain, four conditions are needed. (A) Presence of pain receptors; (B) mediators of the painful stimulus; (C) connection between the receptor and the brain centres that "feel" the pain; (D) effective pain centres (Fig. 1).

2.1 Presence of pain receptors

Pain receptors appear in the dermis at about 8 weeks of gestational age (WGA) and in the mucosae at 10 WGA; they are mature at 20–23 weeks, when they become functional for their connection with the brain [3]. These receptors have nonetheless the same density [4,5] or even a greater density [6] than in adults.

2.2 Mediators of the painful stimulus

Substance P has been found in the spine cord as early as 8–10 WGA [7,8] and encephalin at 12–14 weeks GA [7,9]. The cells that produce endorphins have been detected in the pituitary gland at 12 WGA and their functional maturity is evident at 20 WGA, when they respond to corticotropin-releasing factor stimulation [10].

2.3 Connections between receptors and the brain

The development of pain pathways begins early in the foetus. It is composed of four stages. The first appears in the embryo (6th WGA), where the dorsal horn cells of the spinal cord form synapses with the primordial sensory neurons, that (stage 2) attain the cutis of the limbs, of the rest of the body and of the mucosae at, respectively, 11 [11,12], 15 and 20 WGA [13,14]. Stage 3 is the migration and differentiation from the spinal cord of the neurons that will form the spino-thalamic tract; this takes place in the rat at 12 days of embryonic life [15,16], comparable with a human embryo of 30 days [17].

2.4 Development of the pain assessment centers: the thalamus

The thalamus begins its maturation around 12 weeks [18] and is complete at around 21 weeks [19,20]. The amygdala appears at 12 weeks of gestation and is developed at term [21,22].

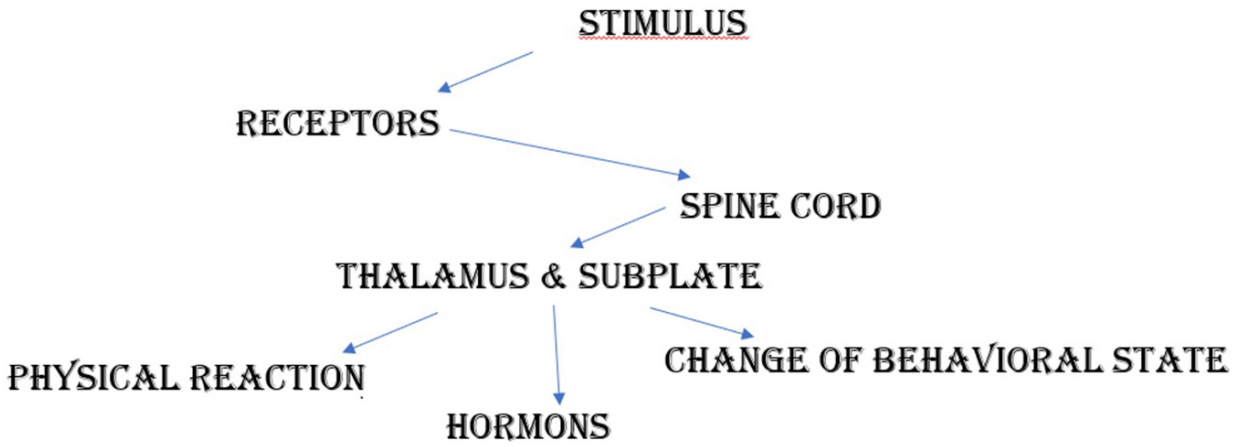

Fig. 1. Pain transmission and effects in midgestation. The cascade of pain starting at midgestation. From the cause to the signs.

2.5 The connections with the cortex

Thalamo-cortical fibres appear at 15–23 WGA [22–24] and attain the subplate at 24 WGA, to progress later to the definitive cortex at 24–32 WGA [25]. This enables the cortex to respond to peripherical stimulations [26]. For other authors, the first subplate projections from the thalamus arrive between weeks 12 and 18 [27,28], the thalamic afferents begin to reach the somatosensory subplate at 20 WGA. The connections from the thalamus arrive to the subplate as early as 12–18 WGA [27,28], then they head the somatosensory and the visual subplate at 20 and 20–22 WGA respectively [29,30], to progress later to the definitive cortex [31].

2.6 Development of pain assessment centers: subplate

Mode Network are present since the 35th WGA [32, 33]; this Network has an important role in the development of consciousness. Nonetheless, even before that, another important brain structure is involved with pain processing: the subplate. It appears early (11th WGA) in human foetuses, becomes prominent at 22–34 WGA, then gradually disappears almost totally at 6 months of postnatal life [27], though some subplate cells are still present in adults [34]. The subplate is a transitory primordial cortex where neurons remain a while until their definitive migration to the mature cortex. It is a carrefour for thalamo-cortical fibers, where the information from the thalamus can be processed [35–37]; it also has a spontaneous electrical activity [38] and has an important role in early human behaviours [39,40].

2.7 Development of the cerebral cortex

Neurons from the subplate are driven to the cortex simultaneously with the arrive of direct fibres from the thalamus to the cortex, starting at around 24 WGA [41]. Then this process increases in speed until the subplate definitively disappears and the cortex is fully developed.

3. Arguments in favor and against foetal pain

3.1 Need for a mature brain cortex

According to some researchers, pain can only be perceived if the patient has a mature and safe brain cortex; nonetheless, others do not agree [42–51], arguing that the mere presence of the periphery-thalamus connection is enough to let pain be perceived. These latter researchers base their argument on the cases of babies with anencephaly. These babies in fact show an unexpected discriminative awareness [50,51]: they disclose an apparent capacity of discriminating people, situations, environments, and are capable of visual orientation and musical preferences. As a matter of fact, several stimuli can be processed without the help of the brain cortex [43,44,49] and provide useful visual information, or trigger complex experiences such as fear [45,52]. This can be true also for pain processing, according to some authors [53,54]: anencephalic foetuses have a withdrawal reaction to pain [55] and similar reactions are described in babies with extensive brain damage [56].

3.2 Responses of the body to the stimulus and behavioural states

Babies born at 26–31 weeks exhibit coordinated facial expressions in response to heel prick, although these are immature compared to older babies [57]. A behaviour similar to infantile crying has been reported in foetuses using 4D-US scan technique [58] and blink-startle reflex in response to a sudden stimulus has been described in 30-week old foetuses [59]. Some wonder whether these reactions may constitute pain or just a response to the stimulus with no negative implications like stress or suffering. In a review of the literature, Mellor [60] argues that foetuses spend a lot of time in sleep, and this would preserve them from pain. But two pieces of evidence contrast with this conclusion: foetal sleep is not continuous and the foetus can be awakened [51,61,62]. Term foetuses spend 9% of the day awake [45]. F3 (calm wakefulness) and F4 (active

wakefulness) states are present in 21% of the day in full term foetuses [63]; several reports show that foetal sheep spend a significant amount of time in wake, during late gestation [64–72]. Even circadian rhythms are present in foetus after their midgestation, in particular with regard to heartbeat and locomotor activity [73]; also the EEG shows a wake pattern after the 30th GAW [74]. External stimulations [75] can wake up even sleeping foetuses [76,77]. It is common knowledge that childbirth, and the manoeuvres that caregivers perform on them at birth, cause awakening in all viable foetuses.

3.3 Intrauterine sedation

According to some authors [60,78], progesterone, prostaglandins and adenosine present in the amniotic fluid cause foetal sedation and therefore analgesia. Nonetheless, this raises some perplexities. The first is the confusion between the terms "sedation" and analgesia": the mere fact that a patient is sedated does not imply that they are not feeling pain. Sedation is a state of diminished awareness, not of analgesia. But there is something more: these neuromodulators, should be at foetal concentrations greater than in mothers' blood to have an actually anaesthetic effect: if mothers' blood values are not enough to be analgesic, a higher level is mandatorily necessary to provoke analgesia in the foetus. But human foetal blood adenosine levels in the third trimester of gestation are only moderately higher than those in mothers' blood (0.58 microM/L [79] vs 0.41 microM/L [80] respectively), though in sheep maternal levels "2–4 folds greater" than in foetal blood are reported [81]. Furthermore, Yoneyama *et al*. [82] showed that blood adenosine levels are higher in pre-eclamptic mothers than in foetuses, though this does not cause analgesia in the mothers. Progesterone is higher in the foetal blood than in maternal blood across pregnancy, but this difference almost disappears at the end of pregnancy: in fact, while foetal progesterone remains constant, maternal progesterone increases with gestational age [83]. We should point out that, though higher than usual, these values are utterly far from being analgesic in mothers, and consequently in foetuses. Prostaglandin D2 has sleep-promoting properties, but the only studies that assess this property are performed by intracerebral infusion [84].

3.4 Endocrine responses to stimuli

Several studies assess the changes in stress hormone production due to pain or stress in foetal animals. The catecholamine system has been studied to investigate if pain provokes an increase of adrenaline/noradrenaline in a similar way as in adults. In effect, stress can provoke an increase of these hormones in animal foetuses during the development period correspondent to the second half of human gestation [85,86]; studies performed on monkeys show that this production is accompanied by long-lasting adverse changes in motor, social and cognitive behaviour [87–90]. Other studies were performed in human foetuses. Stress hormones soar during a blood transfusion performed in human foetuses through their hepatic vein; this increase is not present if the transfusion is performed through the umbilical vein that has no nociceptors [91] and it is also absent if the foetus was previously given opioids [92]. Some authors argue that this does not necessarily mean a response to pain, but just a response to a physical stimulus with no emotional implication. This would mean that anesthetised adults have a similar increase in stress hormones if they receive a painful stimulus during the influence of anaesthesia. On the contrary, adult anesthetized patients show no increases in stress hormones during surgery [93,94]. Marana *et al*. [95] performed a review of the literature showing an increase of stress hormones in patients undergoing surgery, but most of the articles cited assessed their measures in the hours or days after surgery (i.e., including post-surgery stress), but not during surgery [96–98]. Only one article [99], showed an increase in adrenaline and noradrenaline during anaesthesia in adults, but only in the group of patients who underwent a special technique (carbon dioxide insufflation) for laparoscopic resection of ovarian tumours; another paper questioned the effectiveness of low doses of anaesthetics to blunt adrenaline increase in adults, but agrees that high doses are effective in doing it [100]. Painful stimulation causes an increase in catecholamines in anesthetized brain-dead patients, although a missed increase in the control group decreases the strength of this study [101]; moreover, brain death itself can have been the cause of this increase [102].

3.5 Development of foetal consciousness

In the third trimester of gestation, foetuses show signs of some kind of consciousness. To assess this, researchers introduced an auditory paradigm for the investigation of memory traces over different time scales, the so called "local-global" paradigm [103]. The local-global paradigm consists of a sequence of tones which can either contain only identical tones or end with a different tone. In practice, authors studied if foetuses responded with a startle to a new sound inserted in a series of equal sounds (first order regularity violation) or if they responded with a startle when they perceived a new sound sequence after a series of equal sound sequences (second order regularity violation). The detection of an error can be assessed by the event-related P300 component in the electroencephalogram, an endogenous potential due to a person's reaction to the stimulus. In particular, P300 is considered to be developed in mental processes involving the evaluation and categorization of a stimulus. The authors concluded that the foetal assessment of second-order regularity violation is a sign for conscious mental processing [104]. Another sign of likely foetal consciousness is the presence of a rudimental brain Default Mode Network in the last trimester of pregnancy, deputed to consciousness and to the development of empathy and

theory of the mind [27,105]. The Default Mode Network involves several brain areas, as the hippocampus, the parietal lobe, and the angular circumvolution [28]. These data show that the foetus has some kind of consciousness, and this makes its perception of pain to some extent similar to that of an adult.

4. Analgesia for foetal surgery

Two premises should be made to deal with the use of anaesthetics for prenatal surgery.

4.1 The neurotoxicity for the foetus

Attention should be paid to the administration of maternal anaesthetics during the pregnancy [106], due to the risks highlighted in 2016 by the Food and Drug Administration, which suggested not to exceed the 3-hour exposure to anaesthetics for children under the age of 3 years [107]. This group potentially includes the foetal population exposed to anaesthetics during maternal anaesthesia. It is supposed that GABA agonist (propofol, thiopental, isoflurane) and NMDA antagonist drugs (ketamine, nitrous oxide, tramadol) may exert their toxic effect on the developing brain by an action on GABA and glutamate receptors [108,109]. The effects of isoflurane on the developing brain were evaluated using foetal sheep models [108]; pregnant ewes were exposed to single or repeated doses of isoflurane: no significant neuroapoptosis was observed in the single exposure groups, but repeated isoflurane exposure resulted in increased neuroapoptosis of the frontal cortex [108]. Prolonged exposure to isoflurane produced neuroapoptosis in fetal brain [110] as well as in the neonatal brain [111]. The negative effect on foetal heart has been reduced by administration of supplemental intravenous anesthesia (SIVA) with propofol and remifentanil infusions prior to uterine incision [112] or of just remifentanil [113] to the mother: both lower the required amount of desflurane for anaesthesia. Sevoflurane can damage the fetal frontal cortex in mice [114]. Some anaesthetic drugs have a protective effect on the brain and can be useful in preventing the negative effects of anaesthesia in foetuses. Dexmedetomidine has no interaction with GABA or NMDA receptors, and reduces the doses of volatile anaesthetics while providing anxiolysis, hypnosis and analgesia. Bypassing both GABAergic and glutaminergic systems makes dexmedetomidine, an alfa2-agonist, a possible neuroprotector of the foetal brain from isoflurane. This effect has been showed in ovine and foetal rat models [115]. Xenon, a noble gas, is another potentially neuroprotector [116]. Even propofol can give some neuroprotection when used in addition to isoflurane alone [112]; nonetheless, propofol detrimental effects on the developing brain have been extensively described [117].

4.2 Extraction index

The extraction index represents the amount of medication that is removed from the foetal circulation by the placenta and does not arrive to the fetus. In the case of maternal anaesthetics, it varies and can be high; in this case, even though the anaesthetic given to the mother attains good values in her blood, it is not sufficiently high in foetal blood [118,119].

Table 1. Extraction index of the main maternal anaesthetics used during foetal surgery.

Drug	Extraction index (foetal/maternal ratio)
Propofol	0.7–1.3
Ketamine	1.26
Thiopenthal	0.4–1.1
Morphine	0.61–1
Fentanyl	0.5–0.9
Oxycodone	1
Remifentanil	0.29–0.88

Legend: see the text for details. From Ref#123, adapted.

The values available for the foetal/maternal total concentration ratios were approximately 0.3 for bupivacaine and etidocaine, 0.5 for lidocaine, 0.7 for mepivacaine, and 1 for prilocaine [120]. The low ratios of bupivacaine and etidocaine result from extensive binding (90%) of these drugs to maternal alpha1-acid glycoprotein which exceeds corresponding foetal protein binding (50%). The passage of drugs through the placenta depends on various factors, which will affect the concentration of the drug in the foetal blood [120]. These factors are fat solubility, molecular weight and ionic charge of the drug. The highly ionized molecules, the liposoluble ones and those with molecular weight lower than 500 Daltons easily cross the placenta [121]. The passage of the drug also depends on the acidity of the foetal blood, which will be more acidic the more it will favor the passage of non-ionized molecules [121]. For example, lidocaine is a weak base that increases in foetal blood in case of foetal acidosis. Placental transfer of muscle relaxants is very low, with a foetal concentration ~10–20% of the maternal plasma concentration [122]. The extraction indices of halothane, isoflurane and nitrous oxide are 0.71/0.87, 0.71 and 0.7/0.8, respectively [122] and sevoflurane 0.38 [123]; that of propofol ranges 0.5/0.8 [124]; maternal blood concentrations of propofol are 14 times higher than those of foetal blood after 5 min after infusion and twice as high after 180 min [124]. Morphine and fentanyl extraction rate range 0.6–1 and from 0.5–0.9 respectively [123,125,126]. Table 1 summarizes the main evidences.

We should also discuss if the foetus requires a direct or an indirect analgesic treatment.

Several authors endorse a sole analgesia given to the mother to anaesthetise both mother and foetus [127], in particular in the case of laparoscopic surgery [128]. Others suggest an additional foetal direct analgesia should be administered during surgery [129] using opioids. Fentanyl provided intramuscularly to the fetus (10 μg/kg) decreases

the stress responses to painful procedures; in particular, a decrease beta-endorphin response to pain and an absent Doppler US response to pain have been described [130] as well, as it is noted in the case of premature babies [131]. Opioids can be provided to the foetus either via intramuscular injection or via umbilical cord [132,133]. Some investigators recommend administering 20 μg/kg intramuscular fentanyl to the foetus prior to the procedure [134,135], while others recommend giving the mother a continuous infusion rate of 0.1 μg/kg/min remifentanil to achieve foetal immobilization and maternal sedation, although they do not exclude the direct administration of analgesics to the foetus. Intra-amniotic administration of opioids to the foetus has been proposed: researchers have shown that higher plasma concentrations are obtained in foetal lamb than in sheep, suggesting that this pathway could be usable for humans [136].

Last, foetal activity during surgery is worth monitoring, with regard to general suffering and to pain.

The need of foetal monitoring is a tenet in this field. We should be aware if the foetus is undergoing any hypoxemic or painful distress during this kind of surgery. To this aim, we need a continuous monitoring of the foetal heart rate and foetal heart variability, being the latter a sign of sympathetic unbalance [137]. Nonetheless, a change of foetal heart rate variability is not always an indicator of foetal distress but may simply be a sign of expected anaesthetic effects on the foetal autonomic nervous system [138]. Cardiotocography, fetal echocardiography or ultrasound assessment of umbilical or middle cerebral artery blood flow can be monitored for fetal well-being, but interpretation can be difficult [139]. Fetal blood pressure monitoring is not yet feasible [139] Slowing of the fetal heart can be a sign of fetal hypoxaemia and acidosis, but can also be related to a decrease in temperature, maternal respiratory acidosis, or to the administration of drugs [140]. Some authors have tried to create a fetal pain assessment tool, to be used during prenatal surgery [141]. The current fetal monitoring during prenatal surgery is based on echocardiographic monitoring of fetal heart rate and contractility. If any concerns are indicated by the fetal echocardiographic evaluation, more advanced ultrasound monitoring of umbilical and middle cerebral artery are obtained.

5. Conclusions

The arguments in favour of foetal pain and the administration of foetal analgesics during open surgery overweigh those that are against. This should be taken into consideration by those who perform this special type of surgery. Signs of pain in human foetuses are evident from the 20th to 22nd week of gestation and the foetus should receive the same analgesic care during the surgery that a premature baby at an identical postconceptional age receives. Today the debate focuses on the type of anaesthetic to be provided to the foetus and whether administering anaesthetics to the mother is sufficient to guarantee foetal anaesthesia. In this review we have brought valid elements for those who have to perform this type of surgery.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The author declares no conflict of interest.

References

[1] Lönnqvist P. What has happened since the first World Congress on Pediatric Pain in 1988? The past, the present and the future. Minerva Anestesiologica. 2020; 86: 1205–1213.

[2] Derbyshire SW, Bockmann JC. Reconsidering foetal pain. Journal of Medical Ethics. 2020; 46: 3–6.

[3] Narisawa Y, Hashimoto K, Nihei Y, Pietruk T. Biological significance of dermal Merkel cells in development of cutaneous nerves in human foetal skin. Journal of Histochemistry and Cytochemistry. 1992; 40: 65–71.

[4] Gleiss J, Stuttgen G. Morphological and functional development of the skin. In Stave U (ed.) Physiology of the perinatal period (pp. 889–906). Appleton-Century-Crofts: New York. 1970.

[5] Brauer PR. Human embryology: the ultimate USMLE step 1 review. Hanley & Belfus: Philadelphia. 2003.

[6] Fitzgerald M, Butcher T, Shortland P. Developmental changes in the laminar termination of a fibre cutaneous sensory afferents in the rat spinal cord dorsal horn. The Journal of Comparative Neurology. 1994; 348: 225–233.

[7] Charnay Y, Paulin C, Dray F, Dubois PM. Distribution of enkephalin in human foetus and infant spinal cord: an immunofluorescence study. Journal of Comparative Neurology. 1984; 223: 415–423.

[8] Cousins MJ, Carr DB, Horlocker TT, Bridenbaugh PO. Cousin and Brindenbaugh's Neural blockade in clinical anaesthesia and management of pain. 4th edn. Lippincott Williams & Wilkins: Philadelphia. 2009.

[9] de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? Early Human Development. 2006; 82: 257–266.

[10] Li JY, Dubois MP, Dubois PM. Ultrastructural localization of immunoreactive corticotropin, beta-lipotropin, alpha- and beta-endorphin in cells of the human foetal anterior pituitary. Cell and Tissue Research. 1979; 204: 37–51.

[11] Okado N. Onset of synapse formation in the human spinal cord. The Journal of Comparative Neurology. 1981; 201: 211–219.

[12] Larsen WJ, Sherman LS, Potter SS, Scott WJ. Human Embryology. 3rd edn. Churchill Livingstone: Philadelphia. 2001.

[13] Humphrey T. Embryology of the central nervous system: with some correlations with functional development. The Alabama Journal of Medical Sciences. 1964; 1: 60–64.

[14] Valman HB, Pearson JF. What the foetus feels. British Medical Journal. 1980; 280: 233–234.

[15] Altman J, Bayer SA. The development of the rat spinal cord.

Advances in Anatomy Embryology and Cell Biology. 1984; 85: 1–164.
[16] Davidson S, Truong H, Giesler GJ. Quantitative analysis of spinothalamic tract neurons in adult and developing mouse. The Journal of Comparative Neurology. 2010; 518: 3193–3204.
[17] Alicelebić S, Grbesa D. Development of the rat telencephalon–volumetric analysis. Bosnian Journal of Basic Medical Sciences. 2004; 4: 11–14.
[18] Mojsilović J, Zecević N. Early development of the human thalamus: Golgi and Nissl study. Early Human Development. 1991; 27: 119–144.
[19] Molnár Z, Clowry GJ, Šestan N, Alzu'bi A, Bakken T, Hevner RF, *et al*. New insights into the development of the human cerebral cortex. Journal of Anatomy. 2019; 235: 432–451.
[20] Sekulic S, Gebauer-Bukurov K, Cvijanovic M, Kopitovic A, Ilic D, Petrovic D, *et al*. Appearance of foetal pain could be associated with maturation of the mesodiencephalic structures. Journal of Pain Research. 2016; 9: 1031–1038.
[21] Munisamy B. The extended amygdala: embryonic origin and genetic regulation of its development. 2011. Available at: https://repositori.udl.cat/handle/10459.1/63936?show=full (Accessed: 11 February 2022).
[22] Govaert P, Triulzi F, Dudink J. The developing brain by trimester. Handbook of Clinical Neurology. 2020; 171: 245–289.
[23] Kostovic I, Rakic P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. The Journal of Comparative Neurology. 1990; 297: 441–470.
[24] Kostović I, Judas M. The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatrica. 2010; 99: 1119–1127.
[25] Lowery CL, Hardman MP, Manning N, Hall RW, Anand KJ, Clancy B. Neurodevelopmental changes of foetal pain. Seminars in Perinatology. 2007; 31: 275–282.
[26] Kostović I, Sedmak G, Judaš M. Neural histology and neurogenesis of the human foetal and infant brain. Neuroimage. 2019; 188: 743–773.
[27] Bystron I, Blakemore C, Rakic P. Development of the human cerebral cortex: Boulder Committee revisited. Nature Reviews Neuroscience. 2008; 9: 110–122.
[28] Thomason ME, Chang CE, Glover GH, Gabrieli JDE, Greicius MD, Gotlib IH. Default-mode function and task-induced deactivation have overlapping brain substrates in children. NeuroImage. 2008; 41: 1493–1503.
[29] Machado-Rivas F, Gandhi J, Choi JJ, Velasco-Annis C, Afacan O, Warfield SK, *et al*. Normal Growth, Sexual Dimorphism, and Lateral Asymmetries at Fetal Brain MRI. Radiology. 2021; 211222.
[30] Hevner RF. Development of connections in the human visual system during foetal mid-gestation: A DiI-tracing study. Journal of Neuropathology & Experimental Neurology. 2000; 59: 385–392.
[31] Huang H, Zhang J, Wakana S, Zhang W, Ren T, Richards LJ, *et al*. White and gray matter development in human foetal, newborn and pediatric brains. Neuroimage. 2006; 33: 27–38.
[32] Apkarian AV, Bushnell MC, Treede R, Zubieta J. Human brain mechanisms of pain perception and regulation in health and disease. European Journal of Pain. 2005; 9: 463–463.
[33] Moser J, Schleger F, Weiss M, Sippel K, Semeia L, Preissl H. Magnetoencephalographic signatures of conscious processing before birth. Developmental Cognitive Neuroscience. 2021; 49: 100964.
[34] Kostović I, Lukinović N, Judaš M, Bogdanović N, Mrzljak L, Zečević N, *et al*. Structural basis of the developmental plasticity in the human cerebral cortex: the role of the transient subplate zone. Metabolic Brain Disease. 1989; 4: 17–23.
[35] Kostovic I, Judas M. The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatrica. 2010; 99: 1119–1127.
[36] Allendoerfer KL, Shatz CJ. The subplate, a transient neocortical structure: its role in the development of connections between thalamus and cortex. Annual Review of Neuroscience. 1994; 17: 185–218.
[37] Kanold PO, Luhmann HJ. The subplate and early cortical circuits. Annual Review of Neuroscience. 2010; 33: 23–48.
[38] Hanganu IL, Kilb W, Luhmann HJ. Functional synaptic projections onto subplate neurons in neonatal rat somatosensory cortex. The Journal of Neuroscience. 2002; 22: 7165–7176.
[39] Kanold PO, Kara P, Reid RC, Shatz CJ. Role of subplate neurons in functional maturation of visual cortical columns. Science. 2003; 301: 521–525.
[40] Molnár Z, Blakemore C. How do thalamic axons find their way to the cortex? Trends in Neurosciences. 1995; 18: 389–397.
[41] Kostović I, Judas M. Transient patterns of cortical lamination during prenatal life: do they have implications for treatment? Neuroscience and Biobehavioral Reviews. 2007; 31: 1157–1168.
[42] Denton DA, McKinley MJ, Farrell M, Egan GF. The role of primordial emotions in the evolutionary origin of consciousness. Consciousness and Cognition. 2009; 18: 500–514.
[43] Merker B. Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. The Behavioral and Brain Sciences. 2007; 30: 63–134.
[44] Johnson MH. Subcortical face processing. Nature Reviews Neuroscience. 2005; 6: 766–774.
[45] Ohman A, Carlsson K, Lundqvist D, Ingvar M. On the unconscious subcortical origin of human fear. Physiology & Behavior. 2007; 92: 180–185.
[46] Marín-Padilla M. Developmental Neuropathology and Impact of Perinatal Brain Damage. II: white matter lesions of the neocortex. Journal of Neuropathology and Experimental Neurology. 1997; 56: 219–235.
[47] Takada K, Shiota M, Ando M, Kimura M, Inoue K. Porencephaly and hydranencephaly: a neuropathological study of four autopsy cases. Brain & Development. 1989; 11: 51–56.
[48] Shewmon DA, Holmes GL, Byrne PA. Consciousness in congenitally decorticate children: developmental vegetative state as self-fulfilling prophecy. Developmental Medicine and Child Neurology. 1999; 41: 364–374.
[49] Mulckhuyse M, Theeuwes J. Unconscious attentional orienting to exogenous cues: a review of the literature. Acta Psychologica. 2010; 134: 299–309.
[50] Sewards TV, Sewards MA. Visual awareness due to neuronal activities in subcortical structures: a proposal. Consciousness and Cognition. 2000; 9: 86–116.
[51] Pasley BN, Mayes LC, Schultz RT. Subcortical Discrimination of Unperceived Objects during Binocular Rivalry. Neuron. 2004; 42: 163–172.
[52] Morris JS, Ohman A, Dolan RJ. A subcortical pathway to the right amygdala mediating "unseen" fear. Proceedings of the National Academy of Sciences. 1999; 96: 1680–1685.
[53] Mahieu-Caputo D, Dommergues M, Muller F and Dumez Y. Foetal pain. Presse Medicale. 2000; 29: 663–669.
[54] Anand KJ. Foetal pain? Pain Clinical Updates. 2006; 14: 1–8.
[55] Visser GH, Laurini RN, de Vries JI, Bekedam DJ, Prechtl HF. Abnormal motor behaviour in anencephalic foetuses. Early Human Development. 1985; 12: 173–182.
[56] Oberlander TF, Grunau RE, Fitzgerald C, Whitfield MF. Does parenchymal brain injury affect biobehavioral pain responses in very low birth weight infants at 32 weeks' postconceptional age? Pediatrics. 2002; 110: 570–576.

[57] Johnston CC, Stevens BJ, Franck LS, Jack A, Stremler R, Platt R. Factors explaining lack of response to heel stick in preterm newborns. Journal of Obstetric, Gynecologic, and Neonatal Nursing. 1999; 28: 587–594.
[58] Gingras JL, Mitchell EA, Grattan KE. Foetal homologue of infant crying. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2005; 90: F415–F418.
[59] Bellieni CV, Severi F, Bocchi C, Caparelli N, Bagnoli F, Buonocore G, *et al*. Blink-startle reflex habituation in 30-34-week low-risk foetuses. Journal of Perinatal Medicine. 2005; 33: 33–37.
[60] Mellor DJ, Diesch TJ, Gunn AJ, Bennet L. The importance of 'awareness' for understanding foetal pain. Brain Research Reviews. 2005; 49: 455–471.
[61] Nijhuis JG. Foetal behavior. Neurobiology of Aging. 2003; 24: S41–S46; discussion S47–S49, S51–S52.
[62] Pillai M, James D. Behavioural states in normal mature human foetuses. Archives of Disease in Childhood. 1990; 65: 39–43.
[63] Van de Pas M, Nijhuis JG, Jongsma HW. Foetal behaviour in uncomplicated pregnancies after 41 weeks of gestation. Early Human Development. 1994; 40: 29–38.
[64] Ioffe S, Jansen AH, Russell BJ, Chernick V. Sleep, wakefulness and the monosynaptic reflex in foetal and newborn lambs. Pflugers Archiv European Journal of Physiology. 1980; 388: 149–157.
[65] Crossley KJ, Nicol MB, Hurst JJ, Walker DW, Thorburn GD. Suppression of arousal by progesterone in foetal sheep. Reproduction, Fertility and Development. 1997; 9: 767–773.
[66] Jansen AH, Chernick V. Foetal breathing and development of control of breathing. Journal of Applied Physiology. 1991; 70: 1431–1446.
[67] Nicol MB, Hirst JJ, Walker DW. Effect of pregnane steroids on electrocortical activity and somatosensory evoked potentials in fetal sheep. Neuroscience Letters. 1998; 253: 111–114.
[68] Nicol MB, Hirst JJ, Walker DW. Effect of finasteride on behavioural arousal and somatosensory evoked potentials in foetal sheep. Neuroscience Letters. 2001; 306: 13–16.
[69] Rigatto H, Blanco CE, Walker DW. The response to stimulation of hindlimb nerves in foetal sheep, in utero, during the different phases of electrocortical activity. Journal of Physiology. 1982; 4: 175–185.
[70] Ruckebusch Y. Development of sleep and wakefulness in the foetal lamb. Electroencephalography and Clinical Neurophysiology. 1972; 32: 119–128.
[71] Ruckebusch Y, Gaujoux M, Eghbali B. Sleep cycles and kinesis in the foetal lamb. Electroencephalography and Clinical Neurophysiology. 1977; 42: 226–237.
[72] Szeto HH. Behavioral states and their ontogeny: animal studies. Seminars in Perinatology. 1992; 16: 211–216.
[73] Kintraia PI, Zarnadze MG, Kintraia NP, Kashakashvili IG. Development of daily rhythmicity in heart rate and locomotor activity in the human foetus. Journal of Circadian Rhythms. 2005; 3: 5.
[74] Stockard-Pope JE, Werner SS, Bickford RG. Atlas of neonatal electroencephalography. Raven Press: New York. 1992.
[75] Birnholz JC, Benacerraf BR. The development of human foetal hearing. Science. 1983; 222: 516–518.
[76] Zimmer EZ, Divon MY. Foetal vibroacoustic stimulation. Obstetrics and Gynecology. 1993; 81: 451–457.
[77] Leader LR, Fifer WP. The potential value of habituation in the prenate. In Lecanuet JP (ed.) Foetal development: a psychobiological perspective (pp. 83–404). Lawrence Erlbaum Associates Publishers: Hillsdale. 1995.
[78] Lee SJ, Ralston HJ, Drey EA, Partridge JC, Rosen MA. Foetal pain: a systematic multidisciplinary review of the evidence. Journal of the American Medical Association. 2005; 294: 947–954.
[79] Yoneyama Y, Sawa R, Suzuki S, Shin S, Power GG, Araki T. The relationship between uterine artery Doppler velocimetry and umbilical venous adenosine levels in pregnancies complicated by preeclampsia. American Journal of Obstetrics and Gynecology. 1996; 174: 267–271.
[80] Yoneyama Y, Suzuki S, Sawa R, Takeuchi T, Kobayashi H, Takei R, *et al*. Changes in plasma adenosine concentrations during normal pregnancy. Gynecologic and Obstetric Investigation. 2000; 50: 145–148.
[81] Sawa R, Asakura H, Power GG. Changes in plasma adenosine during simulated birth of foetal sheep. Journal of Applied Physiology. 1991; 70: 1524–1528.
[82] Yoneyama Y, Suzuki S, Sawa R, Kiyokawa Y, Power GG, Araki T. Plasma adenosine levels and P-selectin expression on platelets in preeclampsia. Obstetrics and Gynecology. 2001; 97: 366–370.
[83] Donaldson A, Nicolini U, Symes EK, Rodeck CH and Tannirandorn Y. Changes in concentrations of cortisol, dehydroepiandrosterone sulphate and progesterone in foetal and maternal serum during pregnancy. Clinical Endocrinology. 1991; 35:447–451.
[84] Hayaishi O. Molecular genetic studies on sleep-wake regulation, with special emphasis on the prostaglandin D(2) system. Journal of Applied Physiology. 2002; 92: 863–868.
[85] Peters DA. Effects of maternal stress during different gestational periods on the serotonergic system in adult rat offspring. Pharmacology, Biochemistry, and Behavior. 1988; 31: 839–843.
[86] Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Progress in Neurobiology. 2001; 65: 427–451.
[87] Schneider ML. Prenatal stress exposure alters postnatal behavioral expression under conditions of novelty challenge in rhesus monkey infants. Developmental Psychobiology. 1992; 25: 529–540.
[88] Schneider ML, Clarke AS, Kraemer GW, Roughton EC, Lubach GR, Rimm-Kaufman S, *et al*. Prenatal stress alters brain biogenic amine levels in primates. Development and Psychopathology. 1998; 10: 427–440.
[89] Rebsam A, Seif I, Gaspar P. Refinement of thalamocortical arbors and emergence of barrel domains in the primary somatosensory cortex: a study of normal and monoamine oxidase a knockout mice. The Journal of Neuroscience. 2002; 22: 8541–8552.
[90] Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, *et al*. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. Science. 1995; 268: 1763–1766.
[91] Giannakoulopoulos X, Teixeira J, Fisk N, Glover V. Human foetal and maternal noradrenaline responses to invasive procedures. Pediatric Research. 1999; 45: 494–499.
[92] Fisk NM, Gitau R, Teixeira JM, Giannakoulopoulos X, Cameron AD, Glover VA. Effect of direct foetal opioid analgesia on foetal hormonal and hemodynamic stress response to intrauterine needling. Anesthesiology. 2001; 95: 828–835.
[93] Desborough JP. The stress response to trauma and surgery. British Journal of Anaesthesia. 2000; 85: 109–117.
[94] Grass JA. The role of epidural anaesthesia and analgesia in postoperative outcome. Anesthesiology clinics of North America. 2000; 18: 407–428.
[95] Marana R, Margutti F, Catalano GF, Marana E. Stress responses to endoscopic surgery. Current Opinion in Obstetrics & Gynecology. 2000; 12: 303–307.
[96] Engin A, Bozkurt BS, Ersoy E, Oguz M, Gökçora N. Stress hyperglycemia in minimally invasive surgery. Surgical Laparoscopy & Endoscopy. 1998; 8: 435–437.
[97] Yuen PM, Mak TWL, Yim SF, Ngan Kee WD, Lam CWK, Rogers MS, *et al*. Metabolic and inflammatory responses after

laparoscopic and abdominal hysterectomy. American Journal of Obstetrics and Gynecology. 1998; 179: 1–5.
[98] Akhtar K, Kamalky-asl ID, Lamb WR, Laing I, Walton L, Pearson RC, *et al*. Metabolic and inflammatory responses after laparoscopic and open inguinal hernia repair. Annals of the Royal College of Surgeons of England. 1998; 80: 125–130.
[99] Ogihara Y, Isshiki A, Kindscher JD, Goto H. Abdominal wall lift versus carbon dioxide insufflation for laparoscopic resection of ovarian tumors. Journal of Clinical Anesthesia. 1999; 11: 406–412.
[100] Ura T, Higuchi H, Taoda M, Sato T. Minimum alveolar concentration of sevoflurane that blocks the adrenergic response to surgical incision in women: MACBAR. European Journal of Anaesthesiology. 1999; 16: 176–181.
[101] Fitzgerald RD, Hieber C, Schweitzer E, Luo A, Oczenski W, Lackner FX. Intraoperative catecholamine release in brain-dead organ donors is not suppressed by administration of fentanyl. European Journal of Anaesthesiology. 2003; 20: 952–956.
[102] Lopau K, Mark J, Schramm L, Heidbreder E, Wanner C. Hormonal changes in brain death and immune activation in the donor. Transplant International. 2000; 13: S282–S285.
[103] Moser J, Schleger F, Weiss M, Sippel K, Dehaene-Lambertz G, Preissl H. Magnetoencephalographic signatures of hierarchical rule learning in newborns. Developmental Cognitive Neuroscience. 2020; 46: 100871.
[104] Chennu S, Noreika V, Gueorguiev D, Blenkmann A, Kochen S, Ibáñez A, *et al*. Expectation and attention in hierarchical auditory prediction. The Journal of Neuroscience. 2013; 33: 11194–11205.
[105] Thomason ME, Grove LE, Lozon TA Jr, Vila AM, Ye Y, Nye MJ, *et al*. Age-related increases in long-range connectivity in foetal functional neural connectivity networks in utero. Developmental Cognitive Neuroscience. 2015; 11: 96–104.
[106] Olutoye OA, Style C, Menchaca A. Neurocognitive Effects of Foetal Exposure to Anaesthesia. Anesthesiology Clinics. 2021; 39: 851–869.
[107] Food and Drug Administration: FDA Warnings Regarding Use of General Anesthetics and Sedation Drugs in Young Children and Pregnant Women. 2016. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2016/12/fda-warnings-general-anaesthetics-sedation-drugs-young-children-pregnant-women (Accessed: 11 February 2022).
[108] Olutoye OA, Sheikh F, Zamora IJ, Yu L, Akinkuotu AC, Adesina AM, *et al*. Repeated isoflurane exposure and neuroapoptosis in the midgestation foetal sheep brain. American Journal of Obstetrics and Gynecology. 2016; 214: 542.e1–542.e8.
[109] Olutoye OA, Lazar DA, Akinkuotu AC, Adesina A, Olutoye OO. Potential of the bovine brain as a model for anaesthesia-induced neuroapoptosis. Pediatric Surgery International. 2015; 31: 865–869.
[110] Creeley CE, Dikranian KT, Dissen GA, Back SA, Olney JW, Brambrink AM. Isoflurane-induced apoptosis of neurons and oligodendrocytes in the fetal rhesus macaque brain. Anesthesiology. 2014; 120: 626–638.
[111] Noguchi KK, Johnson SA, Dissen GA, Martin LD, Manzella FM, Schenning KJ, *et al*. Isoflurane exposure for three hours triggers apoptotic cell death in neonatal macaque brain. British Journal of Anaesthesia. 2017; 119: 524–531.
[112] Boat A, Mahmoud M, Michelfelder EC, Lin E, Ngampraserttwong P, Schnell B, *et al*. Supplementing desflurane with intravenous anaesthesia reduces foetal cardiac dysfunction during open foetal surgery. Paediatric Anaesthesia. 2010; 20: 748–756.
[113] Marsh BJ, Sinskey J, Whitlock EL, Ferschl MB, Rollins MD. Use of remifentanil for open in utero foetal myelomeningocele repair maintains uterine relaxation with reduced volatile anesthetic concentration. Fetal Diagnosis and Therapy. 2020; 47: 810–816.
[114] Song R, Ling X, Peng M, Xue Z, Cang J, Fang F. Maternal Sevoflurane Exposure Causes Abnormal Development of Foetal Prefrontal Cortex and Induces Cognitive Dysfunction in Offspring. Stem Cells International. 2017; 2017: 6158468.
[115] Laudenbach V, Mantz J, Lagercrantz H, Desmonts J, Evrard P, Gressens P. Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. Anesthesiology. 2002; 96: 134–141.
[116] Lavaur J, Le Nogue D, Lemaire M, Pype J, Farjot G, Hirsch EC, *et al*. The noble gas xenon provides protection and trophic stimulation to midbrain dopamine neurons. Journal of Neurochemistry. 2017; 142: 14–28.
[117] Andropoulos DB. Effect of Anesthesia on the Developing Brain: Infant and Fetus. Fetal Diagnosis and Therapy. 2018; 43: 1–11.
[118] Bellieni CV. Analgesia for fetal pain during prenatal surgery: 10 years of progress. Pediatric Research. 2021; 89: 1612–1618.
[119] Bellieni CV. New insights into fetal pain. Seminars in Fetal and Neonatal Medicine. 2019; 24: 101001.
[120] Nau H. Clinical Pharmacokinetics in Pregnancy and Perinatology. I. Placental transfer and fetal side effects of local anaesthetic agents. Developmental Pharmacology and Therapeutics. 1985; 8: 149–181.
[121] Datta S. Obstetric Anesthesia Handbook (pp. 211–301). 4th Edn. Springer: USA. 2006.
[122] Campbell C, San Vicente M. Placental transfer of Drugs and Perinatal Pharmacology. In Suresh M (ed) Shnider and Levinson's Anesthesia for Obstetrics. Lippincott Williams & Wilkins: USA. 2013.
[123] Zakowski MI, Galler A. The placenta: anatomy, physiology and transfer of drugs. In Chestnut DH, *et al*. (ed) Chestnut's Obstetric Anesthesia: Principles and Practice (pp. 75–94). 5th edn. Elsevier Saunders: Philadelphia. 2014.
[124] Ngamprasertwong P, Dong M, Niu J, Venkatasubramanian R, Vinks AA, Sadhasivam S. Propofol Pharmacokinetics and Estimation of Fetal Propofol Exposure during Mid-Gestational Fetal Surgery: a Maternal-Fetal Sheep Model. PLoS ONE. 2016; 11: e0146563.
[125] Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and Pharmacodynamics of Drugs Commonly used in Pregnancy and Parturition. Anesthesia and Analgesia. 2016; 122: 786–804.
[126] Heikkinen EM, Kokki H, Heikkinen A, Ranta V, Räsänen J, Voipio H, *et al*. Foetal Fentanyl Exposure and Ion Trapping after Intravenous and Transdermal Administration to the Ewe. Basic & Clinical Pharmacology & Toxicology. 2017; 120: 195–198.
[127] Arens C, Koch C, Veit M, Greenberg RS, Lichtenstern C, Weigand MA, *et al*. Anesthetic Management for Percutaneous Minimally Invasive Fetoscopic Surgery of Spina Bifida Aperta: a Retrospective, Descriptive Report of Clinical Experience. Anesthesia & Analgesia. 2017; 125: 219–222.
[128] Van de Velde M, Van Schoubroeck D, Lewi LE, Marcus MAE, Jani JC, Missant C, *et al*. Remifentanil for Fetal Immobilization and Maternal Sedation during Fetoscopic Surgery: a Randomized, Double-Blind Comparison with Diazepam. Anesthesia & Analgesia. 2005; 101: 251–258.
[129] Mayorga-Buiza MJ, Marquez-Rivas J, Gomez-Gonzalez E. Can fetus feel pain in the second trimester? Lessons learned from a sentinel event. Child's Nervous System. 2018; 34: 195–196.
[130] Fisk NM, Gitau R, Teixeira JM, Giannakoulopoulos X, Cameron AD, Glover VA. Effect of direct fetal opioid analgesia on fetal hormonal and hemodynamic stress response to intrauterine needling. Anesthesiology. 2001; 95: 828–835.

[131] Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet. 1987; 1: 62–66.
[132] Van de Velde M, Jani J, De Buck F, Deprest J. Fetal pain perception and pain management. Seminars in Fetal and Neonatal Medicine. 2006; 11: 232–236.
[133] Gaiser RR, Kurth CD. Anesthetic considerations for fetal surgery. Seminars in Perinatology. 1999; 23: 507–514.
[134] Sutton LN. Fetal surgery for neural tube defects. Best Practice and Research in Clinical Obstetrics and Gynaecology. 2008; 22: 175–188.
[135] Gupta R, Kilby M, Cooper G. Fetal surgery and anaesthetic implications. Contin Educ Anaesth Crit Care Pain. 2008; 8: 71–75.
[136] Strümper D, Durieux ME, Gogarten W, Van Aken H, Hartleb K, Marcus MA. Fetal plasma concentrations after intraamniotic sufentanil in chronically instrumented pregnant sheep. Anesthesiology. 2003; 98: 1400–1406; discussion 5A–6A.
[137] Warner LL, Arendt KW, Ruano R, Qureshi MY, Segura LG. A call for innovation in fetal monitoring during fetal surgery. The Journal of Maternal-Fetal & Neonatal Medicine. 2020; 75: 1–7.
[138] Fedorkow DM, Stewart TJ, Parboosingh J. Fetal heart rate changes associated with general anesthesia. American Journal of Perinatology. 1989; 6: 287–288.
[139] Goonasekera C, Skelton VA. Fetal Safety During Fetoscopic Spina-Bifida Repair: Anesthetic Concerns. Journal of Fetal Medicine. 2021; 8: 97–104.
[140] Reitman E, Flood P. Anaesthetic considerations for non-obstetric surgery during pregnancy. British Journal of Anaesthesia. 2011; 107: i72–i78.
[141] Bernardes LS, Carvalho MA, Harnik SB, Teixeira MJ, Ottolia J, Castro D, *et al*. Sorting pain out of salience: assessment of pain facial expressions in the human fetus. Pain Reports. 2021; 6: e882.