(Acta Anaesth. Belg., 2004, 55, 119-123)

Management of fetal pain during invasive fetal procedures A review

W. HUANG, J. DEPREST (*), C. MISSANT, M. VAN DE VELDE

Abstract : In recent years, fetal stress and analgesia draw more and more attention**.** Evidence that fetuses show a significant endocrinological and hemodynamical response to invasive stimuli, and that these responses can be blocked by analgesia, suggests that fetuses experience a stress response, even if this does not signify they experience "pain". Moreover, it is becoming increasingly clear that experiences of pain of a fetus will be "remembered" by the developing nervous system, perhaps for the entire life of the individual, which can probably lead to abnormal behavioural patterns or altered nociception. But up to now, the entire mechanism of fetal stress response and the optimal analgesic drug, dose and route of administration is not so clear.

INTRODUCTION

Pain is a subjective experience occurring parallel to a physiologic response to impeding or actual tissue damage. Experience of pain requires two components: nociception and a subjective, emotional reaction. Nociception requires an intact sensory system, while an emotional reaction requires consciousness. Since the fetus cannot tell us whether he feels pain and since pain cannot be assessed using objective measures, only indirect methods are useful to determine whether or not the fetus feels pain.

The concept of fetal pain and fetal analgesia becomes more and more important since in utero interventions, treating prenatally diagnosed diseases, are rapidly becoming a clinical reality. Thanks to advances in high-resolution ultrasound and other diagnostic techniques, an increasing number of conditions are diagnosed early in gestation, as well as insight into their pathophysiology has been gained. Some of these conditions are life threatening in utero and may benefit from prenatal surgical intervention. Initially, in utero interventions were performed using open surgery on the unborn child. However, miniaturization of endoscopes has revived the interest in fetoscopy and nowadays, fetoscopic surgery has consolidated its place in modern fetal medicine (8). Two types of fetoscopic surgery are usually distinguished. Fetal surgery includes all types of surgery in which direct interventions on the fetus are performed, but only few of them are amendable by endoscopy. The term obstetric endoscopy was proposed for procedures on the placenta, the umbilical cord and fetal membranes. This kind of procedures is not questioned anymore today, and done in high numbers. The most common procedure at our institution today is laser coagulation of chorionic plate vessels for severe mid-gestational twin-to-twin transfusion syndrome (TTTS) (10). In other cases of complicated monochorionic twin pregnancies, endoscopy is also used to carry out selective feticide by means of cord occlusion (7).

Since Robinson and Gregory published their landmark paper in 1981, demonstrating the necessity and safety of analgesia in preterm neonates (25), pain in neonates and adequate analgesia drew more and more attention. Thanks to the outstanding work by ANAND *et al*. and FISK *et al*. (1, 3, 4, 13, 15, 16), it becomes increasingly clear that fetuses experience stress during an invasive procedure and that, as a consequence, the long-term neurodevelopmental status may be affected. Today, publications emerge describing that fetal analgesia can be performed efficiently, eliminating the fetal stress response. It remains unclear whether this results in improved neurodevelopment and improved long-term outcome.

W. HUANG, MD ; J. DEPREST, MD, PhD ; C. MISSANT, MD ; M. VAN DE VELDE, MD, PhD.
Department of Anesthesiology and Center for surgical technology (CHT), UZLeuven, KULeuven, Leuven, Belgium.
(*) Department of Obstetrics and Gynecology and Center for surgical technology (CHT), UZLeuven, KULeuven, Leuven, Belgium.
Correspondence address : Marc Van de Velde, MD, PhD. Director Obstetric Anesthesia and Extra Muros Anesthesia, Department of Anesthesiology, University Hospitals Gasthuisberg, Herestraat 49, B - 3000 Leuven, Belgium. Phone : 0032-16 34 42 70. Fax : 0032-16 34 42 45. E-mail : marc.vandevelde@uz.kuleuven.ac.be

This review focuses on the evidence that fetal pain is a realistic problem, and on the current status of fetal pain management during in utero procedures.

DOES THE FETUS EXPERIENCES PAIN?

The question whether or not a fetus experiences pain is an immense challenge. The issue demands consideration of the physical and psychological basis of being and the relation between the two. There is no objective measurement of 'pain' ; it is a subjective experience. The fetus is unable to tell us if he feels pain, so other evidence must be used to decide whether the fetus feels pain. Because of the obvious difficulties in studying fetal behavior, activation of the hypothalamo-pituitary-adrenal axis (a 'stress response') has been proposed as a surrogate indicator of fetal pain. This has limitations : stress responses do not necessarily signify pain (for example, during exercise the cortisol level increases), and stress responses do not involve the cortex. However, the converse is the null hypothesis, i.e. in the absence of a stress response the fetus is unlikely to experience pain. Also, one could argue that the stress response is more relevant in terms of immediate and long-term sequelae, whether or not this is associated with pain in the fetus (22).

The idea that a fetus will experience stress when an invasive stimulus is imposed on it and therefore analgesia will be necessary, originated from the work by Anand on pre-term neonates (4). The rationale was that if a premature infant was capable of feeling pain, then there is no reason why a fetus of the same gestation should not also feel pain. FISK and his co-workers continued the work and provided direct evidence that the fetus has hormonal and hemodynamic responses to invasive stimuli. They also showed that these responses can be blocked by analgesia (13,15,28).

Hemodynamic response

It is well known from animal studies that the fetus in late gestation has a remarkable capacity to redistribute its blood flow in response to acute stressors (hypoxemia, hemorrhage) to protect its more vital organs, such as brain and myocardium, and this at the expense of other organs such as the gut, kidneys and the extremities (6,30). Similarly, some chronic stressors, such as sustained hypoxemia or prolonged reductions in uterine blood flow were also associated with increased brain blood flow (5,23). In the human fetus, Doppler ultrasonographical studies have shown an association between chronic hypoxemia of intrauterine growth restriction and redistribution of blood flow (12).

FISK and colleagues demonstrated that acute painful stimuli (transgression of the fetal abdominal wall during in utero transfusion) were associated with a significant hemodynamic response in the fetus. This hemodynamic stress response is consistent with redistribution of blood supply to the brain (28).

Hormonal responses

Due to the research work of, largely, ANAND and co-workers, we are aware that pre-term neonates have hormonal stress responses following invasive interventions. These hormonal responses can be prevented by analgesia (1, 3, 4). As a result, similar studies were performed in the unborn child. Activation of the fetal hypothalamic-pituitary-adrenal (HPA) stress response can be assessed by measuring stress hormones such as noradrenalin, cortisol, β-endorphin and corticotrophin.

FISK studied samples obtained prior and following in utero fetal blood transfusion and compared levels of these hormones before transfusion (immediately after access to the fetal circulation is established), with levels at the end of the transfusion (just before the needle is removed). Fetal plasma was obtained during fetal blood sampling for intrauterine transfusion either by needling the fetal intrahepatic vein (IHV) or by needling the placental cord insertion (PCI). Since the PCI is not innervated, no stress response was observed, whereas in fetuses, transfused in the IHV, a significant increase in stress hormones was recorded (15). The fetal HPA system seems functional from at least the beginning of the second trimester. Extremely low-birth-weight pre-term infants show a normal pituitary response to corticotrophin-releasing factor, and a normal adrenal response to ACTH stimulation. Furthermore, suppression at the hypothalamic or pituitary level by prenatal treatment with corticosteroids leads to decreased levels of fetal plasma cortisol concentration (15).

Anatomical considerations

To experience pain, an intact system of pain transmission must be available. Peripheral receptors develop from the seventh gestational week, initially in the fetal face. From 20 weeks gestation, peripheral receptors are present on the whole body surface (31). From 13 weeks gestation, the afferent

system located in the substantia gelatinosa of the dorsal horn of the spinal cord starts developing (24). Development of afferent fibres connecting peripheral receptors with the dorsal horn starts at 8 weeks gestation (20). Spinothalamic connections start to develop from 14 weeks and are complete at 20 weeks gestation, whilst thalamocortical connections are present from 17 weeks gestation and completely developed at 26-30 weeks gestation (19). From 16 weeks gestation pain transmission from a peripheral receptor to the cortex is possible and certainly completely developed from 26 weeks gestation. It is important to note that serotonin releasing inhibitory descending pain fibres only develop following birth (17). It is therefore safe to assume that the fetus feels more pain then the small infant.

Neurophysiological data

A primitive electroencephalogram (EEG) is present from 19 weeks gestation and from 22 weeks gestation on, it is possible to register a continuous EEG. More advanced EEG recordings, such as a sleep/wake pattern, somatosensory evoked potentials and visually evoked potentials are possible from 24 weeks gestation (3,29).

According to the definitions of pain and feeling, a fetus definitely cannot feel pain. But we cannot deny that the fetal nervous system mounts protective responses to tissue injury. Based on the data mentioned previously, we can safely assume that the fetus reacts to painful stimuli from 24 weeks gestation and that it is possible that this occurs from 16 weeks gestation on.

WHY FETAL ANALGESIA ?

According to the definitions of pain and feeling, a fetus definitely cannot feel pain. But we cannot deny that fetal nervous system mounts protective responses to tissue injury. The evidences for early exposure to noxious stimuli resulting in adverse effects on future neural development are increasing. It means that noxious stimulation not necessarily needs to penetrate consciousness in order to substantially alter the course of sensory development.

RUDA reported that localized inflammation during the neonatal period permanently alters neuronal circuits that process pain in the spinal cord (26).

Pre-term neonates who had experienced 4 weeks of NICU (neonate intensive care unit) therapy manifested decreased behavioral responses and increased cardiovascular responses to the pain of a heel prick as compared to neonates born at 32 weeks. Differences in these response patterns were strongly correlated with the number of invasive procedures experienced since birth, rather than other clinical factors (such as age, Apgar score, birth weight, severity of illness, or weight at 32 weeks post-conception) (18). These data suggest that repetitive pain and stress may alter the neurological substrate associated with pain, leading to altered neurobehavioral responses to subsequent pain in pre-term neonates.

According to ANAND's study, repetitive pain in neonatal rat pups may lead to an altered development of the pain system associated with decreased pain thresholds during development (2). Increased plasticity of the neonatal brain may allow these and other changes in brain development to increase their vulnerability to stress disorders and anxiety-mediated adult behaviour. Similar behavioural changes have been observed during the later childhood of ex-preterm neonates that were exposed to prolonged periods of neonatal intensive care.

Recent studies suggest that, although early painful memories are not accessible to conscious recall, they may be encoded in the "procedural memory" and lead to abnormal behavioural patterns or altered sensory processing in later life (21). TADDIO *et al.* demonstrated that children undergoing a ritual circumcision immediately after birth (without pain relief) react much more vigorously to painful stimuli later in life, such as vaccination at two months of age (27).

It is becoming increasingly clear that experiences of pain will be "remembered" by the developing nervous system, perhaps for the entire life of the individual. These findings should focus the attention of clinicians on the long-term impact of early painful experiences, and highlight the urgent need for developing therapeutic strategies to manage neonatal and fetal pain; otherwise, future generations will pay the price for medical procedures performed today.

MANAGEMENT OF FETAL PAIN DURING IN UTERO PROCEDURES

Because fetal pain is a realistic problem and it is better to error on the safe side, we must provide or attempt to provide adequate pain relief during every situation in which the unborn child may experience potentially painful stimuli.

FISK's study showed that direct administration of 10µg/kg fentanyl intravenously to the fetus

blunts the fetal stress response to intrauterine needling. The magnitude of the β-endorphin and cortisol response was halved, and the cerebral Doppler response was ablated (13). So fetal analgesia is possible and may prevent long-term effects.

During open fetal surgery under maternal general anesthesia, inhalational agents are considered to provide adequate fetal anesthesia and produce uterine relaxation essential for successful surgery. So additional analgesia for the fetus is unnecessary. Direct fetal administration of fentanyl and pancuronium is reserved for cases where the fetus moves during the procedure (14).

Some endoscopic procedures performed directly on the fetus, such as tracheal occlusion to treat congenital diaphragmatic hernia or intrauterine repair of meningomyelocoele, are usually performed under maternal local or regional anaesthesia. Since these procedures do not require maternal general anaesthesia, additional fetal anaesthesia is desired and is usually done by direct administration of opioids and muscle relaxants to the fetus. Injections of these drugs in the umbilical cord or intramuscularly in the fetus are two possible routes of administration.

The term obstetric endoscopy was proposed for procedures on the placenta, the umbilical cord and fetal membranes. Obstetric endoscopic procedures do not require direct contact with the fetus. The risks of maternal (and consequently fetal) general anaesthesia are unlikely to be justified by the degree of stress response inflicted on the fetus. However, immobilisation of the fetus is required to prevent accidental fetal movements complicating these procedures. In these instances fetal immobilisation is possible using maternally administered sedative drugs such as diazepam. However recently, we determined that remifentanil in doses as low as 0.1 μg/kg/min produces effective maternal sedation and fetal immobilisation during these procedures (11).

Some authors even suggest providing analgesia to the unborn child in very specific situations, such as late pregnancy termination, painful fetal conditions and during vaginal delivery, especially during instrumental vaginal delivery (9,17). At this moment, potential side effects of analgesia outweigh the theoretical advantages, so we cannot advise on its routine use in these specific situations. Only during late pregnancy termination, we would advise to provide fetal analgesia prior to the initiation of termination.

Conclusion

From 24 weeks gestation, and probably already from 16 weeks on, the fetus reacts to potentially painful stimuli. These painful stimuli most likely induce long-term neurodevelopmental changes. To prevent long term effects and from an ethical point of view, we have the obligation to explore effective analgesic strategies to manage fetal pain effectively and safely. At present, simple administration of analgesic drugs, devoid of maternal and fetal side effects, is not yet feasible. In fact, only the first publications are emerging, indicating that effective fetal analgesia blunts the acute fetal stress response. Whether these strategies are capable of preventing the long-term effects, is far from clear. Further research should therefore focus on the effectiveness of various strategies to prevent the acute and long-term effects of fetal pain.

Acknowledgments

This work was supported by a 2002 SARB grant for experimental research and by a "Krediet aan Navorsers" (nr. 1.5.080.03) granted by the Fund for Scientific Research Flanders (Fonds voor Wetenschappelijk Onderzoek Vlaanderen).

Dr. Wei Huang is a pre-doctorate student at the Catholic University of Leuven (KULeuven).

References

1 Anand K.J., Barton B.A., McIntosh N., *et, al., Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates*, Arch. Pediatr. Adolesc. Med., **153**, 331-338, 1999.

2 Anand K.J., Coskun V., Thrivikraman K.V., Nemeroff C.B., Plotsky P.M., *Long-term behavioral effects of repetitive pain in neonatal rat pups*, Physiol. Behav., **66**, 627-637, 1999.

3 Anand K.J., Hickey P.R., *Pain and its effects in the human neonate and fetus*, N. Engl. J. Med., **317**, 1321-1329, 1987.

4 Anand K.J., Sippell W.G., Aynsley-Green A. *Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response*, Lancet, **8524**, 62-66, 1987.

5 Boyle D.W., Lecklitner S., Liechty E.A., *Effect of prolonged uterine blood flow reduction on fetal growth in sheep*, Am. J. Physiol., **270**, R246-253, 1996.

6 Cohn H.E., Sacks E.J., Heymann M.A., *et al., Cardiovascular responses to hypoxemia and acidemia in fetal lambs*, Am. J. Obstet. Gynecol., **120**, 817-824, 1974.

7 Deprest J.A., Evrard V.A., Van Schoubroeck D., Vandenberghe K., *Endoscopic cord ligation in selective feticide*, Lancet, **348**, 890-891, 1996.

8 Deprest J.A., Gratacos E., *Obstetrical endoscopy*, Curr. Opin. Obstet. Gynecol., **11**, 195-203, 1999.

9 Deprest J.A., Lerut T.E., Vandenberghe K., *Operative fetoscopy: new perspective in fetal therapy ?*, PRENAT. DIAGN., 17, 1247-1260, 1997.
10 Deprest J.A., Van Schoubroeck D., Van Ballaer P.P., Flageole H., Van Assche F.A., Vandenberghe K., *Alternative technique for Nd: YAG laser coagulation in twin-to-twin transfusion syndrome with anterior placenta*, ULTRASOUND. OBSTET. GYNECOL., **11**, 347-352, 1998.
11 Dewolf J., Deprest J., Schoubroeck V., Devlieger R., Lewi L., Teunkens A., Van de Velde M.. Eur. J. ANAESTHESIOL., **20** [Suppl30], A-586, 2003.
12 Di Renzo G.C., Luzi G., Cucchia G.C., Caserta G., Fusaro P., Perdikaris A., Cosmi E.V., *The role of Doppler technology in the evaluation of fetal hypoxia*, EARLY HUM. DEV., **29**, 259-267, 1992.
13 Fisk N.M., Gitau R., Teixeira J.M., Giannakoulopoulos X., et al., *Effect of direct fetal opioid analgesia on fetal hormonal and hemodynamic stress response to intrauterine needling*, ANESTHESIOLOGY, **95**, 828-835, 2001.
14 Gaiser R.R., Kurth C.D., *Anesthetic considerations for fetal surgery*, SEMIN. PERINATOL., **23**, 507-514, 1999.
15 Giannakoulopoulos X., Sepulveda W., Kourtis P., *et al*., *Fetal plasma cortisol and beta-endorphin response to intrauterine needling*, LANCET, **344**, 77-81, 1994.
16 Gitau R., Fisk N.M., Glover V., *Human fetal and maternal corticotrophin releasing hormone responses to acute stress*, Arch. Dis. CHILD FETAL NEONATAL ED., **89**, F29-32, 2004.
17 Glover V., Fisk N.M., *Fetal pain: implications for research and practice*, BR. J. OBSTET. GYNAECOl., **106**, 881-886, 1999.
18 Johnston C.C., Stevens B.J., E*xperience in a Neonatal Intensive Care Unit affects pain response*, PEDIATRICS, **98**, 925–930, 1996.
19 Kostovic I., Goldman-Rakic P.S., *Transient cholinesterase staining in the mediodorsal nucleus of the thalamus and its connections in the developing human and monkey brain*, J. COMP. NEUROL., **219**, 431-437, 1983.
20 Okado N., *Onset of synapse formation in the human spinal cord*, J. COMP. NEUROL., **201**, 211-219, 1981.
21 Porter F.L., Grunau R.E., Anand K.J., *Long-term effects of pain in infants*, J. DEV. BEHAV. PEDIATR., **20**, 253-61, 1999.
22 Smith R.P., Gitau R., Glover V., Fisk N.M., *Pain and stress in the human fetus*, EUR. J. OBSTET. GYNECOL. REPROD. BIOL., **92**, 161-165, 2000.
23 Richardson B., Korkola S., Asano H., Challis J., Polk D., Fraser M., *Regional blood flow and the endocrine response to sustained hypoxemia in the preterm ovine fetus*, PEDIATR. RES., **40**, 337-343, 1996.
24 Rizvi T., Wadhwa S., Bijlani V., *Development of spinal substrate for nociception*, PAIN [Suppl], **4**, 195, 1987.
25 Robinson S., Gregory G.A., *Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants*, ANESTH. ANALG., **60**, 331-334, 1981.
26 Ruda M.A., Ling Q.D., Hohmann A.G., Peng Y.B., Tachibana T., *Altered nociceptive neuronal circuits after neonatal peripheral inflammation*, SCIENCE, **289**, 628-631, 2000.
27 Taddio A., Katz J., Ilersich A.L., Koren G., *Effect of neonatal circumcision on pain response during subsequent routine vaccination*, LANCET, **349**, 599-603, 1997.
28 Teixeira J.M., Glover V., Fisk N.M., *Acute cerebral redistribution in response to invasive procedures in the human fetus*, AM. J. OBSTET. GYNECOL., **181**, 1018-1025, 1999.
29 Torres F., Anderson C., *The normal EEG of the human newborn*, J. CLIN. NEUROPHYSIOL., **2**, 89-103, 1985.
30 Toubas P.L., Silverman N.H., Heymann M.A., *et al*., *Cardiovascular effects of acute hemorrhage in fetal lambs*, AM. J. PHYSIOL., **240**, H45-48, 1981.
31 Valman H.B., Pearson J.F., *What the fetus feels*, BR. MED. J., **280**, 233-234, 1980.