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Fetal Pain

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Chapter 6

Summary, discussion and future perspectives

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Invasive fetal procedures continue to gain wider applications. An increasing number of fetal diseases become amenable to prenatal intervention, with increasing success rates in terms of survival. However, there is a lack of knowledge on fetal awareness, stress responses and possible fetal pain resulting from these invasive procedures.
This thesis describes the results of our study on fetal stress hormone reactions to intrauterine transfusions and the possibilities for analgesia. Hemodynamic and hormonal changes were measured in fetal blood, before and after intrauterine transfusions, in which the mother received either remifentanil or placebo.

In **chapter 1**, the motives leading to the studies presented in this thesis are described. The Leiden University Medical Centre (LUMC) is the referral centre for invasive fetal therapy in the Netherlands. During invasive procedures, some form of maternal analgesia is usually provided. There is increasing evidence that the fetus could also benefit from analgesia as the fetus has been shown to react to painful stimuli with both hemodynamic and stress hormone changes. However, surprisingly, all we know about fetal stress hormone response to painful stimuli, is based on the results of just one study group [1]. We therefore designed our study in order to evaluate fetal stress and pain in our own patient population.

The fact that pain is a subjective experience makes it extremely difficult to study in fetuses. We cannot simply ask the fetus whether it is in pain. Thus, in order to answer the question whether or not a fetus is capable to experience at least stress, one has to search for alternative measurements. As we describe in **chapter 2**, one can approach the question from different points of view. We discuss the concept of 'pain', as well as the criteria one has to meet to be able to perceive pain. As the fetus is a developing being, it seems reasonable that the fetus is not capable of feeling pain from the very beginning (because it needs some form of awareness to be able to perceive anything at all). However, it is still unclear at what gestational age the fetus is mature enough to be able to react to a painful stimulus. The fetal anatomic, neurophysiologic and behavioural development and responses which are thought to be required to experience pain are discussed. Looking at neuroanatomical maturation, it seems reasonable to assume that at least from the second half of pregnancy the central nervous system of the fetus should be mature enough to process a painful signal [2-5].

Electroencephalography shows that the anatomical pathways are also functioning from this time onward: the fetus starts to show sleep-wake patterns on EEG [6].
Looking at fetal behaviour, fetuses are known to exhibit a withdrawal reflex following a noxious stimulus. This reflex of course does not necessarily imply pain, however with the neuroanatomical maturation and functionality of the system in mind it seems reasonable to assume that the reflexive withdrawal could be regarded as indeed a sign of stress or even pain.

Exploring the hemodynamic changes following a noxious stimulus (**chapter 3**), we saw no differences in transfusions through the intrahepatic portion of the umbilical vein (IHV, in which the fetal abdomen is transgressed with a needle) or the umbilical cord root at placental cord insertion (PCI, in which nerve fibres are absent and therefore no painful stimulus can be present).
In a large cohort of patients undergoing intrauterine transfusions (IUTs) we measured the pulsatility index of the middle cerebral artery (MCA PI) directly before and after IUT. MCA PI is a measure of vascular resistance, known to be decreased in for instance growth restricted fetuses. These fetuses redistribute their blood to their most vital organs, which effect is also known as the 'brain-sparing' effect [7]. In our study we found a similar brain-sparing effect in both groups: MCA PI decreased significantly after IUT, irrespective of site of transfusion. We concluded that it is unlikely that this decrease is caused by a stress reaction due to a noxious stimulus, as it occurred in both groups with absence of the noxious stimulus in the PCI group. We concluded that the changes were most likely caused by the volume expansion during IUT. However, we speculate that the observed decrease in MCA PI in both groups could also be interpreted as a sign that intrauterine transfusion per se is stressful to the fetus and therefore leads to a decreased intracranial vascular resistance independent of the site of transfusion.

We explored the changes in levels of fetal stress hormones noradrenalin, beta-endorphin and cortisol during intrauterine transfusions in both IHV and PCI (**chapter 4**). In a randomised controlled trial, we measured stress hormone levels in a group of fetuses treated with the analgesic remifentanil, and compared these with a group receiving placebo. In both groups, about half of the transfusions were given in the IHV and the other half through the PCI. We concluded that the stress hormone changes are independent of both site of transfusion and the use of remifentanil. However, we

have to mention here that unfortunately only after completion of the study we discovered that the dosage of remifentanil was accidently set at 0.08 µg/kg/min instead of the planned 0.15 µg/kg/min. This dosage was so low, that we expect it will not have any analgesic effect on the fetus. Therefore we restricted us to a detailed description of the results in the placebo group.

Interpretation and generalization of these results has to be done with caution. Some of the limitations of our study are that, first; the population studied consists of (sometimes severely) anaemic fetuses. It is theoretically possible that anaemia might pose a certain level of stress for the fetus, meaning that at the beginning of the transfusion the stress hormone levels could already be elevated [8]. We did indeed measure pretransfusion concentrations of the fetal stress hormones at the higher end of what has been described as normal values in the limited literature on this subject [9, 10].

Secondly, it is known that chronic stress can alter acute stress reactions superimposed on the already existing stress [11]. Therefore, if the fetus would be already somewhat stressed at the beginning of the transfusion, it might be less able to mount an appropriate stress response to another stressful stimulus.

Thirdly, the posttransfusion sample is taken after a significant amount of blood is transfused into the fetal circulation. Although part of that amount leaves the fetal circulation very rapidly after the procedure, the total fetoplacental blood volume is increased with an average of 30% [12]. This could have led to a dilution of the stress hormone concentrations. This could mean that where we measured no differences in concentrations of beta-endorphin and cortisol, in fact the absolute amounts did perhaps rise after the IUT. However, the fact remains that we observed no differences in stress hormone changes in transfusions in either the IHV or PCI. This could mean:

1. Intrauterine transfusions are stressful for the fetus, irrespective of the site of transfusion. Perhaps volume load per se is stressful.
2. The fetus is already stressed because of its anaemic state and is not capable of mounting a further stress reaction
3. Intrauterine transfusions are not stressful or painful for the fetus. After all, it is usually just a single puncture with a thin needle.

These possible confounding factors currently prohibit us to make a definite statement about fetal pain as a genuine entity. Our results do not confirm nor deny that the fetus is capable to react to a potential painful stimulus, or to show signs of stress or

even pain. However, previous research has suggested that presumably painful fetal conditions can lead to alterations in stress reactions after birth. For instance, infants with prenatally diagnosed unilateral hydronephrosis are described to show hypersensitivity of the abdominal skin on the affected side [13]. Even more, the threshold for feeling pain is significantly lower on the affected side than on the unaffected side and this persists for at least three months after corrective surgery. As post-conceptual age increases, an increase of this threshold would be expected (as the capacity of the neonate to distinguish between painful and painless stimuli is maturing). However, in infants with unilateral hydronephrosis this increase did not occur, even on the unaffected side of the abdomen. This suggests that exposure to noxious stimuli in fetal life somehow disrupts the normal nociceptive development resulting in changes that are still present several months after birth and even after corrective surgery.
In the 1980s the Barker hypothesis was formulated, in which Barker and colleagues demonstrated the correlation between low birth weight and death at adult age from ischemic heart disease [14]. This correlation led to the development of a theory called fetal programming [15]. Fetal programming is the phenomenon encompassing deviations from the normal developmental pattern. These deviations enhance risks for disease later in life. There is concern that adverse events during fetal life might lead to fetal programming [16], as for instance the altered pain responses in neonates with prenatally diagnosed hydronephrosis seems to suggest. So let us assume that the fetus is indeed capable of experiencing stress or pain.

If fetal pain is believed to be a genuine entity, the next step is to provide adequate fetal analgesia when performing invasive procedures on the fetus. In **chapter 5** we describe the placental passage of remifentanil during IUT in the second and early third trimester. Remifentanil was administered intravenously to pregnant women undergoing IUTs and remifentanil concentrations in fetal plasma before and after IUT were compared. We could show that the placental passage of remifentanil is 33%, in the second and early third trimester. It is unknown, and one may argue impossible to know which concentration of remifentanil is required to achieve fetal analgesia, but the maternal concentration was very low, leading us to suspect that with a placental passage of 33%, adequate fetal analgesia was unlikely to be achieved. It is however interesting, that previous research has described that fetal immobilisation can be achieved with a tolerable maternal dosage of remifentanil. We are not certain that

immobilising the fetus also means that the fetus experiences no stress or pain, but it seems plausible. As the results of our study suggest that the placental passage is only 30% in the second and early third trimester, one could conclude that the fetus would need a lower amount of remifentanil to achieve analgesia as compared to adults. This is of interest, because children and even newborns require the same amount as adults [17, 18].

Stress or pain

In this thesis, we described several strategies to evaluate fetal stress, in order to gain insight into possible long-term effects of fetal invasive procedures. However, it should be noted here that stress is not necessarily a surrogate for pain. Stress is the stimulus that threatens to destabilize homeostasis within an individual and the stress reaction is the physiologic and behavioural adaptations needed to return to homeostasis. This means that stress not only occurs when an individual is in pain, because both negative and positive stressors can lead to stress, and stress is not necessarily harmful. Stress occurring during birth for instance is thought to be not harmful, and even beneficial to the child, as it probably facilitates rapid adaptation to effectively transition between two extremely different environments [19].
However, in fetal invasive procedures a painful stimulus which is usually not present is inflicted on the fetus. Therefore, it seems plausible that the stress reaction due to these procedures is probably not beneficial for the developing fetus.

Epigenetics

A fundamental question in stress research is how (hormonal) stress reactions can change their action from protection to damage. In a healthy condition the stress system is a highly reactive system that quickly responds to stressors. If the stress system responds slowly, or when stress reactions persist, its mediators enhance vulnerability to disease for which the individual is predisposed. Maladaptive stress responses may result in maladaptive physiologic and behavioural changes [20]. Currently, much effort is made to understand how for instance nutrition or other environmental stimuli can influence developmental pathways during critical periods of

prenatal and postnatal life and thereby apparently induce permanent changes in chronic disease susceptibility.

The underlying biological mechanisms are poorly understood, however it seems likely that epigenetic mechanisms are involved in the developmental origins of health and disease. Epigenetics is the study of inherited changes in phenotype or gene function that occur without a change in the DNA sequence. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism; instead, non-genetic factors cause the organism's genes to behave differently: DNA carries the code of heritable properties, whereas epigenetic modifications dictate the access to this code.
Barker described the correlation between low birth weight and death at adult age from ischemic heart disease. This phenomenon, called fetal programming, could well be explained by singular maternal effects: the intrauterine environment in growth-retarded fetuses is probably far from ideal. However, the children of children born with low birth weight also have an increased risk for ischemic heart disease [21]. This fact can probably only be explained by epigenetic factors. The genome of growth restricted fetuses is probably epigenetically modified to be prepared for possible poor conditions after birth and is not prepared for the comparative excess it actually meets after birth [22, 23]. This leads to an increased risk for ischemic heart disease. The epigenetic modifications are then carried on in offspring: epigenetic programming can remain intact for multiple generations. This is of course a concern in fetuses undergoing invasive procedures or who are likely to be persistently stressed because of presumably stressful or painful conditions. Perhaps it is indeed possible for fetal invasive procedures to have an effect not only on the fetus itself but also on generations to come.

Recommendations for future research

Future studies on fetal stress hormones should focus on stress hormone reactions following invasive procedures more invasive than transgressing the fetal body with just a thin needle, for instance, following shunt placement in case of fetal hydrothorax or bladder outlet obstruction.

As with anaemic foetuses, foetuses with hydrothorax or bladder outlet obstruction could very well be chronically stressed due to their illness. This should be taken into account. Nonetheless, we feel it is still valuable to assess their stress response because the stimulus is considerably larger than the thin needle used for intrauterine transfusions.
Shunt placement usually does not include fetal blood sampling. Cordocentesis with the sole purpose to collect fetal stress hormone samples is clearly unethical, given the fact that all extra invasive procedures involve an additional risk for complications. Therefore, in these procedures the stress hormone samples should be taken from the amniotic fluid. In humans, there is some literature on both normal values of stress hormones in amniotic fluid and values in presumably chronic painful conditions, such as gastroschisis [24-26]. To our knowledge, there is no literature on fetal stress hormone reactions following an acute stressful stimulus so this would be valuable to assess.

Future studies should search for safe and adequate means of acquiring fetal analgesia. Fetal analgesia should be safe for both mother and fetus, and ideally it would provide analgesia to them both through intravenous infusion in the mother. Especially when no access to the fetal circulation is made, for instance for shunt placements in fetal thorax or bladder, transplacental fetal analgesia seems the most elegant method.
However, given the fact that not all analgesics cross the placenta completely or even partly, one should also investigate other routes of administration. Medication could be administered directly into the fetal circulation, as has been previously described for fentanyl [27]. However, when given in the intrahepatic portion of the umbilical vein, this would mean losing the benefit of achieving fetal analgesia before administering a painful stimulus to the fetus. Direct intramuscular administration has the same disadvantage as intrahepatic venous injection and another drawback is the prolongation of the procedure in order to await absorption. Animal studies have shown that intra-amniotic injection of analgesics can provide subtherapeutic levels in the fetus, however one has to await the fetus swallowing the fluid before absorption takes place thus prolonging the procedure even more [28].

Future studies should also focus on which medication to use to achieve fetal analgesia. In humans, attempts so far included fentanyl and remifentanil. These are both opioids, which are known to have possible undesirable side effects. For example, early opioid exposure has been suggested to increase subsequent responses to painful

stimuli and enhance the chances for addictive and self-destructive behaviour later in life [29, 30]. However, remifentanil is ultra-short working, so perhaps it does not have these classic opioid disadvantages [31-34].We need to elucidate the possible harmful effects of remifentanil and search as well for alternatives that are safe for both mother and fetus. Acetaminophen (paracetamol) is considered safe for both mother and fetus and does not have the side-effects described for opioids. Acetaminophen is described to cross the placenta, which makes it an interesting candidate to evaluate its fetal analgesic potential [35, 36].
With regard to long term consequences of fetal stress or pain, further research is needed into health and coping strategies at adult age and the role of epigenetic dysregulation in disease.

In conclusion, pain will always remain difficult to study in fetuses because of its subjective nature. It is possible to measure stress hormone reactions as a surrogate of pain, but the question will always remain if stress responses are beneficial or harmful for the developing fetus. However, there is concern about fetal programming or epigenetic dysregulation following adverse events during fetal life. Thus our conviction is that we need to search for safe methods to achieve adequate analgesia in both mother and fetus for fetal invasive procedures.

With the current understanding of fetal pain and fetal analgesia we would advocate the following:

1. Fetal analgesia for invasive procedures should be provided from at least 20 weeks gestation onwards
2. All invasive fetal procedures warrant fetal analgesia, but in procedures involving more than just a single puncture with a thin needle it is obligatory.
3. Analgesics should be given intravenously to the mother. The drug of choice should be ultra-short working (like remifentanil) therefore minimising possible undesirable side-effects to both fetus and mother.

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