Fetal Pain

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Chapter 1

General introduction and outline of this thesis

General introduction

The question is not
Can they reason?
Nor, can they talk?
But, can they suffer?

(The eighteenth century philosopher, Jeremy Bentham, wrote this about animals. It caused a change in attitude towards animals and their treatment that is continuing to day, such that in the UK even frogs and fishes are required by Act of Parliament to be protected by anaesthesia from possible suffering due to invasive procedures)

Ever since I started working at the Prenatal Diagnosis and Therapy unit of the Leiden University Medical Centre, I have wondered how much fetuses can feel and how much they notice from the procedures we perform on them. Leiden is the referral centre for fetal therapy in the Netherlands. For various indications we perform invasive procedures such as intrauterine transfusions and shunt placement in the fetal thorax or bladder. At a yearly basis, approximately 120 invasive procedures are performed in our centre. If you observe the puncturing of the fetal abdomen for intrahepatic transfusions, you can hardly believe that the fetus remains unaware of what is happening. Most fetuses move vigorously when punctured with a needle, which intuitively seems to suggest that like born children, the unborn child is also capable of experiencing pain. In all invasive fetal procedures, maternal analgesia is warranted. But how about fetal analgesia?

Until the second half of the last century, premature infants were thought to be unable to perceive pain and therefore were usually operated on without analgesia. Because neonates may not have memories of painful experiences, they were thought to be incapable of interpreting pain in a similar matter as adults [1-3]. And because providing anaesthesia for small premature infants was so problematic due to circulatory

instability, many physicians recommended using no anaesthesia as the technique of choice [4]. In 1981 Robinson and Gregory published their landmark paper demonstrating the necessity and safety of analgesia in preterm neonates [5]. They introduced anaesthesia with intravenous narcotics for ligation of the patent ductus arteriosus in small infants and demonstrated hemodynamic stability in these children during surgery. But still, rather than basing themselves on physiologic data, they stated that their use of anaesthesia was based on 'philosophic objections' to no anaesthesia at all. Thanks to the work by Anand et al there came further understanding of pain perception in newborns [6]. Anand described that numerous lines of evidence suggest that in the neonate (and even in the late gestation human fetus), pain pathways as well as cortical and subcortical centres necessary for pain perception are well developed. Thanks to his work, it became increasingly clear that even premature infants experience stress during invasive procedures and that, as a consequence, their long-term neurodevelopmental status might be affected [7-9]. Both hyperalgesia and hypoalgesia have been described following neonatal injury, not only on the site of injury but also over the whole body [10].

Nowadays it is unthinkable to perform invasive procedures on newborns without proper analgesics. We know now that an infant of for example 30 weeks gestation is indeed able to feel pain [11]. But does the same hold true for a fetus of the same gestation? Fisk et al performed several studies in which they showed that the fetus is able to show a hemodynamic and circulatory stress response to possible painful procedures [12-17]. This does not mean per se that the fetus is also capable of feeling pain, because stress and pain are of course not the same. Stress is the stimulus that threatens to destabilize homeostasis within an individual and the stress reaction is the adaptations needed to return to this homeostasis. 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. But as we cannot directly measure pain, stress is probably the second best to achieve insight into the fetal wellbeing.

The fetal environment is quite different from the neonatal environment and some researchers feel that the fetus is constantly in a somewhat sleep-like state, under influence of endogenous neuroinhibitors produced by both fetus and placenta and not able to be disturbed by anything at all [18-20]. They state that the fetus is not capable to experience stress or pain. But clearly this does not comply with our observation that most fetuses quite distinctly react to a painful stimulus. When punctured with a needle, the fetus almost invariably turns his body away from the

needle. This reaction seems too complex to be a mere reflexive response, as some feel that it reflects [21]. Even more so, previous research has suggested that exposure to noxious stimuli in fetal life somehow disrupts the normal nociceptive development which is still noticeable several months after birth [22]. This implies that stressful or painful experiences during fetal development can result in long-term changes in the fetal central nervous system that may alter future perception, behaviour and responses to painful stimuli.
It is known that maternal stress during pregnancy can lead to an increased susceptibility to psychopathology in their offspring [23]. Efforts are made to minimise maternal stress during pregnancy, so why not try to minimise fetal stress as well?

Leiden University Medical Centre as fetal therapy unit

Since 1965, Leiden has been the national referral centre for the treatment of fetal anaemia based on red blood cell immunisation. The first transfusions were given to the fetus intraperitoneally, but since 1987 the transfusions are performed intravascular [24, 25]. In the subsequent years, more indications for fetal therapy were added, for instance intravascular transfusion of platelets in the fetus with neonatal alloimmune thrombocytopenia (NAITP) or intravascular transfusion of red cells for fetal anaemia due to parvovirus B19 infection [26, 27].
In the last decade, the field of fetal medicine has really evolved. In 2000, the first fetoscopic lasercoagulation of the interplacental anastomoses in twin-to-twin-transfusion syndrome (TTTS) in monochorionic twins was performed in Leiden [28]. Intrauterine fetal shunting for lower urinary tract obstructions (LUTO) or congenital cystic adenomatoid malformation (CCAM) was introduced in 2002 and new applications for invasive fetal procedures are being developed currently [29-32].

Outline of the thesis

The question I have always asked myself was whether or not an invasive procedure is potentially harmful for the fetus and if so, whether or not analgesia could be beneficial. Intuitively, I would say that the fetus should receive adequate analgesia when punctured with a needle. Surprisingly, all we know about fetal stress reactions to painful stimuli is based on the findings of just one study group [33-36]. We therefore

designed our own study in order to look for signs of fetal stress and pain in our own patient population. We measured the hemodynamic and hormonal changes in fetuses undergoing transfusions for fetal anaemia and aimed to test whether or not maternally administered remifentanil gives adequate fetal analgesia.

The studies in this thesis can be summarized as follows:

Chapter 2 – Review of the current knowledge of fetal stress and pain.

Chapter 3 – Study to assess the fetal hemodynamic changes in transfusions in either the intrahepatic portion of the umbilical vein or the placental cord insertion.

Chapter 4 – Study to assess the changes in concentrations of the fetal stress hormones noradrenalin, beta-endorphin and cortisol in intrauterine transfusions in both the intrahepatic portion of the umbilical vein and the placental cord insertion, in which either remifentanil or placebo was administered to the mother.

Chapter 5 – Study to assess the placenta passage of remifentanil.

Chapter 6 - General discussion and summary concerning all studies of the thesis.

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