

# Perinatal factors and hearing outcome

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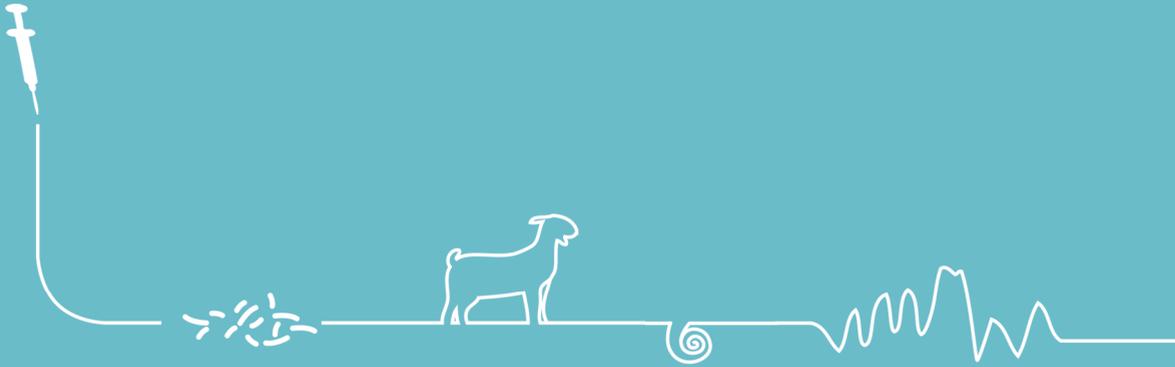
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# CHAPTER 8

Valorisation addendum



## Valorisation addendum

### ***Relevance and implications***

#### *Scientific relevance*

According to recent estimates of the World Health Organization, more than 5% of the world's total population suffer from some form of disabling hearing loss (WHO, 2012). Besides this, sensorineural hearing loss is the most common congenital disorder, with a prevalence of 1 in every 1000 newborns in the Western World.<sup>235</sup> This thesis aims at the analysis of perinatal risk factors for hearing loss in childhood.

Since the introduction of national hearing screening programs in the western world, early identification of hearing loss has improved tremendously in the last decade.<sup>275</sup> Infants with a positive hearing screening tests are referred for total audiological examination. Depending on the etiology and level of hearing loss, the management of these children ranges widely; audiological, medical/surgical, educational and (re)habilitation methods, and child & family support.<sup>276</sup> Evidence is accumulating that early hearing loss interferes with or disrupts typical auditory cortical development by delaying or preventing the formation of neuronal connections and the maturation of cortical layers.<sup>277</sup> This underlines the need for early identification of hearing loss to be able to restore or improve auditory input to the brain within a sensitive period for auditory cortical development.<sup>278</sup>

Besides early identification of the actual hearing loss, a greater understanding of risk factors for congenital hearing loss is needed with regard to preventive strategies. Although the survival of preterm infants over the last decade has been improved by advances in perinatal care, the prevalence of major neonatal and long-term morbidities like hearing loss in this group has not significantly changed.<sup>1</sup> In this thesis we tried to gain insight in perinatal risk factors for auditory impairment.

First of all, the effect of an intrauterine LPS-infection to the auditory system was investigated (Chapter 2). In an animal model of LPS induced chorioamnionitis fetal perilymphatic inflammation was demonstrated as well as small changes to the auditory brainstem responses after birth (Chapter 3). The association between histological chorioamnionitis and adverse neonatal hearing screening was not confirmed in our study of two clinical cohorts of preterm born babies (Chapter 4). However, Hirose et al. recently showed that systemic LPS had direct effects on the blood-labyrinth barrier and induced signs of cochlear inflammation in a mice model.<sup>242</sup> While LPS alone did not affect hearing, animals that received LPS prior to ototoxic agents had worse hearing loss and more hair cell injury compared to those that received saline pretreatment.<sup>243</sup> Regarding the outcome of our studies, a multi-hit model was hypothesized to exert deleterious effect to the auditory pathway by intrauterine infection. This is of major interest for future studies examining hearing outcome in relation to intrauterine inflammation as we know that a chorioamnionitis is

present in ~10% of term infants, in about 50% of very low birth weights infants (VLBW) and up to 80% of the extremely low birth weight infants (ELBW).<sup>24</sup>

Secondly, the effect of perinatal asphyxia on hearing outcome was analyzed in the second part of this thesis. Perinatal hypoxic–ischemic insults, which occur in 1–6 per 1000 live full-term births, is considered as one of the major risk factors for auditory impairment<sup>17</sup> and severe neurological sequelae in newborn infants.<sup>14–16</sup> However, clinical studies do not agree on the exact role of perinatal asphyxia and related variables in hearing outcome and evidence of intervention in this process to protect the auditory pathway from these effects is scarce. In a late-preterm lamb model, we showed the effect of perinatal asphyxia to the auditory brainstem parameters (Chapter 5). A protective effect to the ABR parameters was demonstrated by ante- and postnatal propofol anesthesia compared to isoflurane anesthesia. This outcome is in line with other experimental data suggesting that drugs given during a therapeutic window after a hypoxic-ischemic event may be of value in designing otoprotective strategies in near future. Keeping in mind that hearing impairment has major implications for quality of life, this underlines the medical and socio-economic relevance of this outcome.

In the last part of this thesis, the feasibility of ultra-high MR imaging was evaluated in the preterm ex vivo temporal bone. By the introduction of ultra high resolution MR imaging of the inner ear<sup>52, 55</sup> and the application of MR imaging even in fetal conditions<sup>56, 57</sup> new possibilities have been created to evaluate the inner ear in relation to several factors. We showed that 7TMR imaging gave high quality detailed images of the fluid filled structures of the preterm lamb temporal bone ex vivo (Chapter 6). This tool may allow for the evaluation of subtle inner ear disorders and the effect of interventional therapies in experimental animal protocols or in human clinical settings in future.

### ***Economic relevance***

Permanent hearing loss not only disrupts acquisition of spoken language, but also affects other domains of neurocognitive development, e.g. cognitive, social and academic functioning and by this constitutes a particularly serious obstacle to optimal development and education.<sup>4, 5</sup> It has been estimated that untreated deaf infants can cost society approximately \$1,126,300 over the course of their lifetime.<sup>279</sup> The outcome of this thesis will contribute to a better understanding of the risk factors of hearing loss in children and by this, might help in potential otoprotective strategies in perinatal care. Reducing the incidence of neurodevelopmental morbidities by advances in perinatal care can be of great socio-economic value for the society.

### ***Innovation***

Within this thesis we explored scientific boundaries between research areas of congenital sensorineural hearing loss and perinatal medicine. By this, groundbreaking hypothesis

about the risk factors for hearing loss were analyzed and put in perspective. We introduced an original sheep model to analyze the effect of intrauterine inflammation and hypoxia-ischemia on the peripheral and central auditory pathway. The chronically instrumented fetal ovine model is widely used to observe fetal neurological outcome under a range of stimuli like LPS exposure<sup>43-45</sup> and hypoxia-ischemia.<sup>46, 47</sup> Application of this model to a broader set of questions concerning the perinatal and postnatal integrity of the auditory pathway is of interest to elucidate the relationship between perinatal factors and early hearing outcome.<sup>50, 51</sup>

### ***Target groups***

The unique topics within this thesis are of interest to a wide range of physicians. We have to keep in mind that in about 30% of children with confirmed hearing loss at least one additional disability is demonstrated.<sup>280</sup> This underlines the multidisciplinary care for this group of children with neurodevelopmental disabilities including hearing loss. Also epidemiologists may be interested in this thesis. By nature, the highest risk for early hearing loss with a nongenetic etiology is amongst preterm NICU graduates. Most of the studies analyzing risk factors within this population do rely on retrospective data and frequently include only a small number of infants who develop sensorineural hearing loss. This is even more complicated by the dependency of several variables such as indicators of immaturity or illness severity. For the general population, a better understanding of risk factors for hearing difficulties in childhood is important in providing appropriate treatment and management for the deaf and hearing-impaired infants to help them to have similar opportunities in society alongside as other children.

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