ENGLISH SUMMARY

Prematurity, defined as birth before 37 weeks of gestation, is a major cause of mortality and morbidity in the neonatal period but also beyond. It was the largest single cause of death in children under five in 2016, responsible for almost 1 million deaths worldwide. Especially infants with a birth weight below 1500 grams (Very Low Birth Weight Infants) are at risk for an adverse outcome. Morbidity in the short term is caused by immaturity of practically all organ systems and the immune systems and includes cerebral hemorrhage, respiratory distress syndrome, necrotizing enterocolitis (NEC) and sepsis. Long-term morbidity is a result of complications suffered during the neonatal period and as a consequence of being exposed to extra-uterine life during a critical period of (brain) development. The ultimate goal of neonatal (intensive) care is to achieve that premature infants not only survive the neonatal period but also that they grow up to be healthy adolescents and adults who are able to participate in society. However, from a cohort study of 1338 VLWB and/or infants born before 32 weeks in 1983 that were followed prospectively we know that a substantial part of these individuals suffer from the long-term sequelae of their preterm birth. At 19 years of age 32% of these young adults had moderate to severe problems in neurosensory functioning, neuromotor functioning and/or participation in society. These results stress the need to understand the causes for neurodevelopmental delay after premature birth and to search for novel strategies to ameliorate the condition.

Clearly the cause of neurodevelopmental delay after prematurity is complex and multifactorial. In cases where there are no major abnormalities such as cystic periventriculair leukomalacia (PVL) or intra-ventricular hemorrhage, neurodevelopmental delay can be attributed to diffuse white matter injuries with consecutive maturational disturbances in brain development. The etiology of these white matter injuries (WMI) is not completely understood but systemic inflammation, caused by e.g. sepsis and NEC, seems to play an important role. Therefore, interventions that reduce the incidence of NEC and/or sepsis are likely to have beneficial effects on neurodevelopmental outcome.

The associations of feeding VLBW infants with expressed breast milk of their own mother and a reduced incidence of sepsis and NEC are very well documented. However, especially during the first few days after premature birth, milk of the own mother is often unavailable. Pasteurized donor milk is often given to these infants in an attempt to let them benefit from the favorable effects of human milk. There are several randomized trials dating back to the 1970’s and 1980’s on the effects of donor milk in premature neonates. However, during the HIV epidemic in the 1990’s the majority of donor milk banks closed after the discovery that the virus could be transmitted through breast milk. Since reliable screening methods for the detection of the virus in potential milk donors have become available, milk banks are reopening again. But since the 1980’s the field of neonatology has changed considerably and the effects of donor milk in modern medicine are uncertain due to a lack of randomized controlled trials. We
are in need of high quality meta-analysis before making pasteurized donor milk the standard of care when milk of the own mother is not available.

Furthermore, in recent years it has become apparent that a major determinant of later neurocognitive functioning is related to malnutrition during the neonatal period. Provision of adequate amounts of substrate in the first period of life is amongst others hindered by limited tolerance to enteral substrates. Interventions to increase tolerance to enteral substrates and more knowledge about the specific needs will therefore further improve neonatal outcome. In Chapter 1 of this thesis we give a general introduction on the structural and functional immaturity of the intestine after premature birth. Furthermore it contains a clarification on the properties of human milk and its immunomodulating effects. Chapter 2 gives a broad overview of stable isotope and mass spectrometry techniques that can be used in pediatric and neonatal research to study a broad range of topics such as energy expenditure, macronutrient requirements and inborn errors of metabolism. Stable isotopes techniques are very useful for use in the NICU as they are relatively non-invasive and measurements can be done in excretions like saliva and urine or in very small amounts of blood. In Chapter 3 we show by the use of a dual isotope infusion technique that the splanchnic tissues extract almost all of the dietary aspartate, a non-essential amino acid, in preterm infants. We further show that the majority of the labeled carbon is recovered in expired breath, making it most likely that the sequestered carbon skeleton of aspartate is utilized for energy generation. This stresses the need to supply enterally fed premature neonates with adequate amounts of non-essential amino acid in order to prevent that excessive amounts of essential amino acid are used for energy generation and are therefore not available for tissue generation. Chapter 4 explains a method to determine intestinal permeability in preterm infants. It describes how this method can be used to study the effects of a (nutritional) intervention on intestinal permeability. Chapter 5 describes the results of a randomized controlled clinical trial on the effects of adding insulin-like growth factor 1 (IGF-1) to preterm formula. In this trial patients received either standard infant formula or standard infant formula supplemented with IGF-1, which is also present in human milk and is believed to stimulate gut growth and function. Although gut permeability was significantly lower in the IGF-1 supplemented group on day 14 of life compared to the control group, there were no effects on clinical outcome parameters such as days to full enteral feeding, days to regain birth weight and growth rate. We conclude therefore that our data do not support IGF-1 supplementation to infant formula. In Chapter 6 we show in an observational study that there is a strong association between the intake of mother’s own milk during the first days of life and the incidence of sepsis, NEC and all cause mortality during the first 2 months of life. Chapter 7 is the most recent ESPGHAN position statement and a summary of the available evidence on the use of donor milk. In Chapter 8 we show that a large part (84%) of women that have delivered their child in the VU medical centre (a tertiary hospital) and that subsequently initiate breast feeding, use medication. As also described in chapter 7, there is a lot unknown about the safety and farmacokinetics of the different types of medication during lactation. When premature
neonates receive donor milk they usually receive milk from multiple donors and are thereby potentially exposed to low doses of several types of medication. Strict screening and selection of milk donors is very important but we also conclude that more research on the pharmacokinetics and safety of the most commonly used drugs during breast feeding is necessary. In Chapter 9 we describe the results of the ‘Early Nutrition Study’, a double blind randomized controlled trial on the effects of donor milk feedings compared to formula during the first 10 days of life. In this trial we included a total of 377 infants but were unable to show any beneficial effects on the combined incidence of sepsis, NEC or all cause mortality. Although the study was not designed for this purpose it showed that infants who received the majority of their feedings as own mother’s milk had a better outcome compared to the infants who received the majority of their feedings as formula or donor milk. In Chapter 10 we reflect on the potential reasons why the Early Nutrition Study potentially did not show beneficial effects.

The main conclusions derived from the studies of this thesis are:
- After premature birth all efforts should be made to ensure the infant receives as much milk of the own mother as possible
- Supplementing premature infants with donor milk when milk of the own mother is not (sufficiently) available during the first 10 days of life does not result in a lower incidence of sepsis, NEC and all cause mortality compared to formula feeding
- Addition of IGF-1 to formula does not result in improved clinical outcome parameters such as days to full enteral feeding, days to regain birth weight and growth rate
- The splanchnic tissues extract a large part of aspartate in the first pass and this is subsequently used for energy generation