# Optimising neonatal management of haemolytic disease of the foetus and newborn

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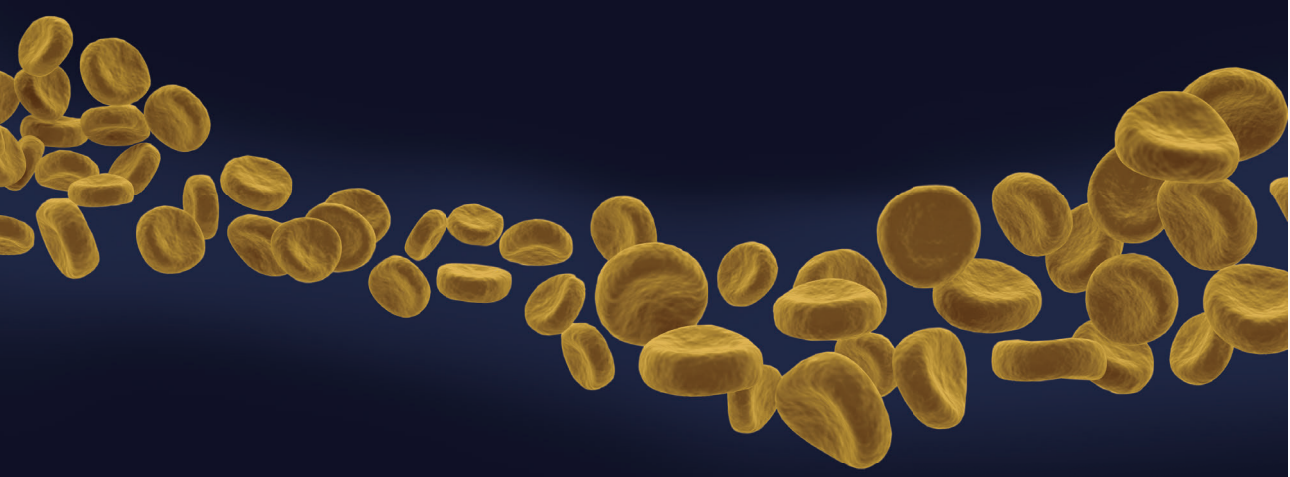
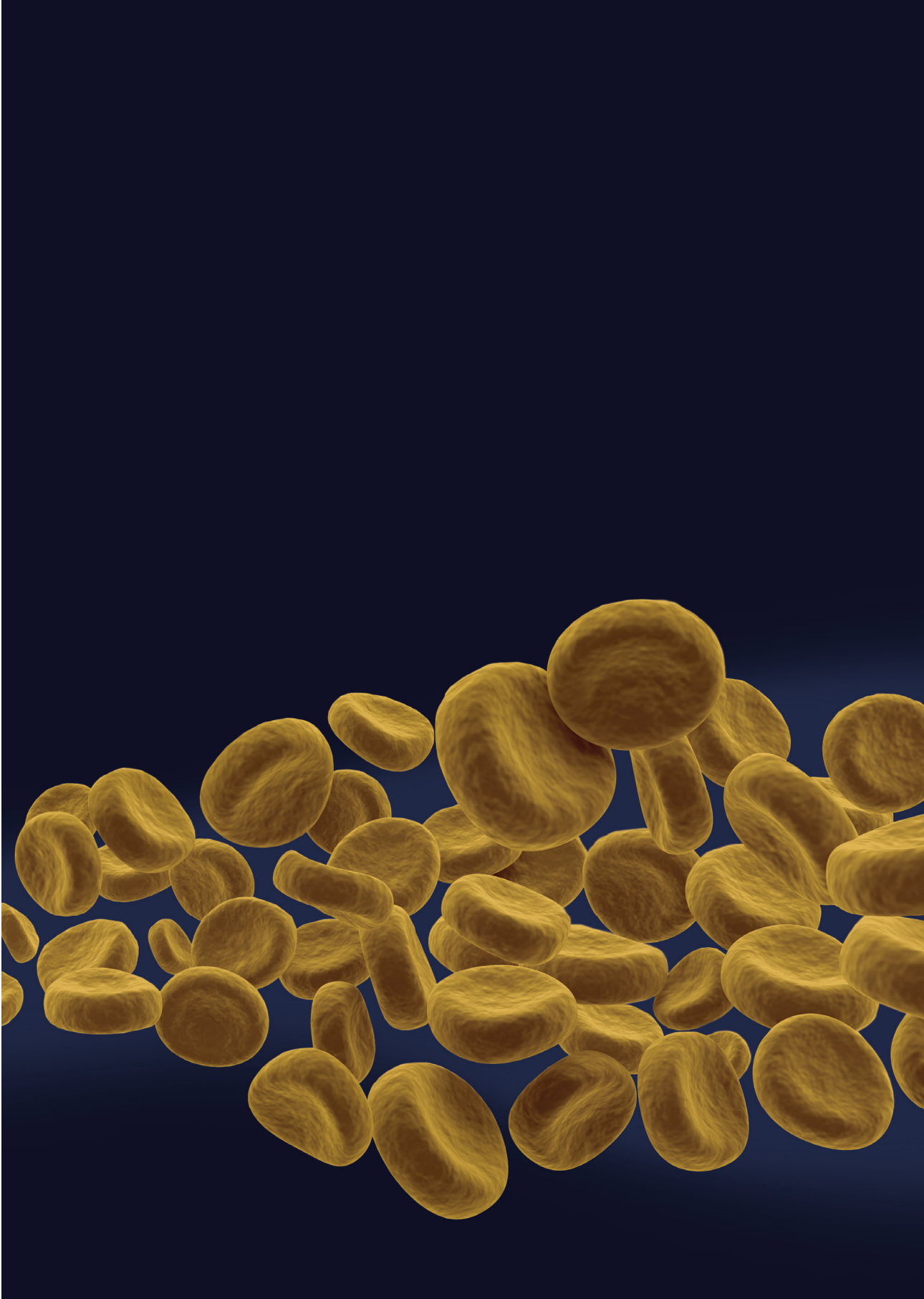
# Part 5 - Summary and discussion





# Summary

Haemolytic disease of the foetus and newborn (HDFN) is a condition in which the red blood cells of the foetus and the newborn child are destructed due to maternal alloantibodies, a process named haemolysis. Haemolysis in HDFN is caused by antibodies formed by the maternal immune system in response to contact with foreign blood group antigens, which can occur due to blood transfusion, or due to foetal-maternal transfusion during pregnancy. Maternal antibodies of the IgG class are actively transported over the placenta and if these reach the foetal circulation, haemolysis can occur if the foetal red blood cells express the recognised blood group antigens. If maternal alloantibodies reach sufficient high levels in the foetal circulation and if the antibodies are biologically active, anaemia can develop already in early pregnancy. In case of severe anaemia, it can be necessary to perform one or more blood transfusions to the anaemic foetus, so called intrauterine transfusions (IUTs).

After birth, a major complication of HDFN is hyperbilirubinaemia. Bilirubin is a waste product of haemoglobulin which is released from the destructed red blood cells and can cause neurological damage if it is present in excessive amounts. The first step in the treatment of hyperbilirubinaemia is intensive phototherapy. Phototherapy transfers bilirubin to a water-soluble form which can be more easily excreted by the kidneys and stool. If the level of bilirubin does not decrease rapidly enough under phototherapy, an exchange transfusion is the next step to remove excessive bilirubin from the circulation. During an exchange transfusion, the blood of the child is replaced with donor blood. Exchange transfusion gives a rapid decrease in bilirubin, but is also a complex procedure with potential complications.

The anaemia that can occur during pregnancy due to HDFN, can also continue weeks to months after birth. Although the connection between the foetal and maternal circulation is lost after birth, there is only a gradual decline in maternal antibodies in the child and therefore these antibodies continue to cause haemolysis for some time. In addition to continued haemolysis, anaemia in HDFN after birth is also caused and prolonged by a transfusion-induced disturbance of the physiological compensatory capacity of the bone marrow in response to anaemia. Despite a distinct decline in red blood cells, the bone marrow fails to adequately regenerate new red blood cells in response. The majority of children with severe HDFN therefore needs one or more red blood cell transfusions in the first three months after birth.

This thesis outlines the course and outcomes of HDFN after birth and provides starting points to further individualise the treatment of HDFN.

## General

In **Chapter 1** an overview is given of the current management of HDFN and the available therapeutic options. The two cornerstones of treatment after birth are firstly the treatment of hyperbilirubinaemia, and therefore the prevention of neurological damage, and secondly, timely recognition of anaemia and treatment with one or more red blood cell transfusions during the first three months after birth. This chapter reviews the literature on well-known therapies such as intensive phototherapy, exchange transfusions and red blood cell transfusions, but also discusses current evidence for alternative therapies, such as treatment with exogenous erythropoietin (EPO) to treat anaemia.

## Predictors of severe disease

**Chapter 2** contributes to the early identification of children with a high risk for severe HDFN. In the foetus and after birth, children affected by HDFN have excessive bilirubin accumulation in the circulation compared to healthy foetuses and children. Before birth, a part of this excessive bilirubin is transported to the maternal circulation via the placenta and is therefore deemed less harmful than in the newborn child. However, it is unclear whether the levels of bilirubin that are measured in the foetus are indeed harmless and how these vary between foetuses affected by HDFN. In this study, the foetal bilirubin levels were assessed, as measured before the administration of an IUT. This study showed that these foetal bilirubin measures are of predictive value for the treatment course after birth, as high foetal bilirubin values are associated with a higher risk for treatment with exchange transfusion. Such predictors can help parents and caregivers to anticipate for severe illness after birth.

In **Chapter 3** the effect of IUT on the foetal and neonatal erythropoiesis was assessed by measuring the foetal and neonatal reticulocytes and by evaluating the need for top-op transfusions after birth. Normally, when the red blood cell count declines, the bone marrow is stimulated by feedback systems to generate more reticulocytes (immature red blood cells) to compensate and prevent anaemia. Erythropoietin is important in this process. In HDFN the destruction of red blood cells can outrun the compensatory capacity of the bone morrow, leading to anaemia which makes it necessary to perform one or more IUTs during pregnancy. This study shows that IUTs, despite the necessity for the immediate treatment of anaemia, disturb the compensatory mechanism of the bone marrow. After an IUT, an exponential decline in reticulocyte formation is observed. Children that were treated with IUTs during pregnancy, need more blood transfusions after birth and are longer transfusion-dependent compared to children not treated with IUTs.

## Neonatal treatment and complications

As described in Chapter 1, the primary aim of treatment in HDFN is the treatment of hyperbilirubinaemia after birth with phototherapy and, if necessary, exchange transfusion. **Chapter 4** gives an overview of treatment with exchange transfusion in children with HDFN in the LUMC, of the last twenty years. The use of exchange transfusion has lowered considerably during this time due to improvement of care. The percentage of children with HDFN that needed one or more exchange transfusions has decreased from 67% to 10%, without an increase in complications.

Neonatal care also includes the management of postnatal anaemia. **Chapter 5** describes how 88% of children affected by HDFN that were treated with one or more IUTs, are also in need of one or more blood transfusions after birth. Of children with HDFN that did not require IUT treatment during pregnancy, 60% is in need of one or more blood transfusions after birth. To detect anaemia timely, the haemoglobin levels of all children affected by HDFN are assessed weekly during the first three months after birth. This study contributes to the identification of so called 'predictors', which might prevent unnecessary and intensive follow-up measures in the future. These specific characteristics can potentially be used to create individual risk profiles in order to fine-tune and individualise postnatal care.

As described under Chapter 5, anaemia is a complicated aspect of HDFN, with a long period of monitoring after birth and usually one or multiple readmissions to administer blood transfusions. **Chapter 6** describes the protocol of a randomised controlled trial conducted at the LUMC, which aims to evaluate the effect of exogenous erythropoietin (EPO) on the prevention of postnatal anaemia in HDFN, as potential alternative for red blood cell transfusions. Erythropoietin is a naturally occurring hormone that in the body stimulates the bone marrow to produce red blood cells. In this study, children are randomised between conventional treatment (weekly haemoglobin measures and, if necessary, a red blood cell transfusion) and conventional treatment combined with weekly home visits and a weekly subcutaneous injection of darbepoetin alfa (Aranesp®, a form of erythropoietin). The hypothesis is that children treated with EPO will need less red blood cell transfusions during the first three months after birth, compared to children in the control group. This study will clarify whether EPO should be part of the standard management of HDFN to prevent anaemia after birth.

Necrotising enterocolitis (NEC) is a severe gastrointestinal condition that can occur in newborns. Although the risk to develop NEC is typically the highest among premature children

and children with (very) low birth weights, there is also a potential association between HDFN and the occurrence of NEC. **Chapter 7** reports on the occurrence of NEC among children with HDFN in the LUMC, as compared to admitted children without HDFN and gives details of the affected children and the disease course. Whereas only 1.3% (4/317) of children with HDFN developed NEC, a mere 0.4% (11/2967) of children without HDFN developed NEC. HDFN is therefore a possible distinct risk factor for NEC. Caregivers should be aware of this risk, especially in children with other risk factors such as prematurity and a low birth weight.

## Long-term outcomes

**Chapter 8** finally describes the long-term outcomes of children treated during pregnancy with one or more IUTs due to HDFN. Of these children between the age of 6 and 12 years, academic and behavioural functioning were assessed by evaluation of school performance reports, school progress data (grade repetition, special-needs education or additional support in school) and behavioural functioning as reported by parents and caregivers or teachers, in comparison with the Dutch norm data. The returned questionnaires and school progress data, showed favourable and reassuring outcomes regarding academic and behavioural functioning after treatment with IUTs. School performance levels for reading comprehension, spelling and mathematics showed a normal distribution and were similar for the study population and Dutch norm data, performance levels were even higher for mathematics compared to norm data. In behavioural functioning, as reported by parents and teachers, a similar incidence was observed of behavioural difficulties in children with HDFN and the norm data. In this study cohort no children attend special-needs education, as opposed to 2.6% in the Dutch norm population. In this cohort 16 children (23%) received or receive additional support in school in the form of speech therapy, support for dyslexia, or physical therapy.



## Conclusion

Due to improved prevention and an efficient national screenings program, HDFN is an increasingly rare disease. This thesis evaluates the current therapy of exchange transfusion for hyperbilirubinaemia (Chapter 4) and describes exogenous erythropoietin as potential new therapeutic agent to treat anaemia (Chapter 6). It also gives starting points to individualise the treatment of these children in the future, as predictive values were identified for a more severe neonatal disease course, complicated with exchange transfusion(s) and/or red blood cell transfusion(s). Predictive values outlined in this thesis are high foetal bilirubin values (Chapter 2) and treatment with multiple IUTs during pregnancy (Chapter 3 and 5). In addition to short-term outcomes measures after birth, the long-term effects of IUTs were also critically evaluated (Chapter 8).