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

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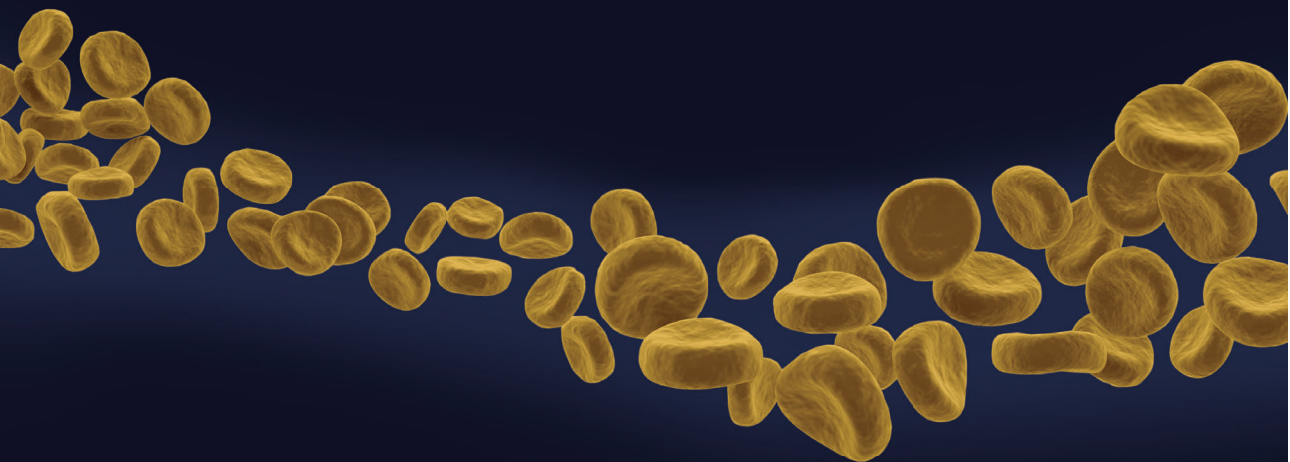
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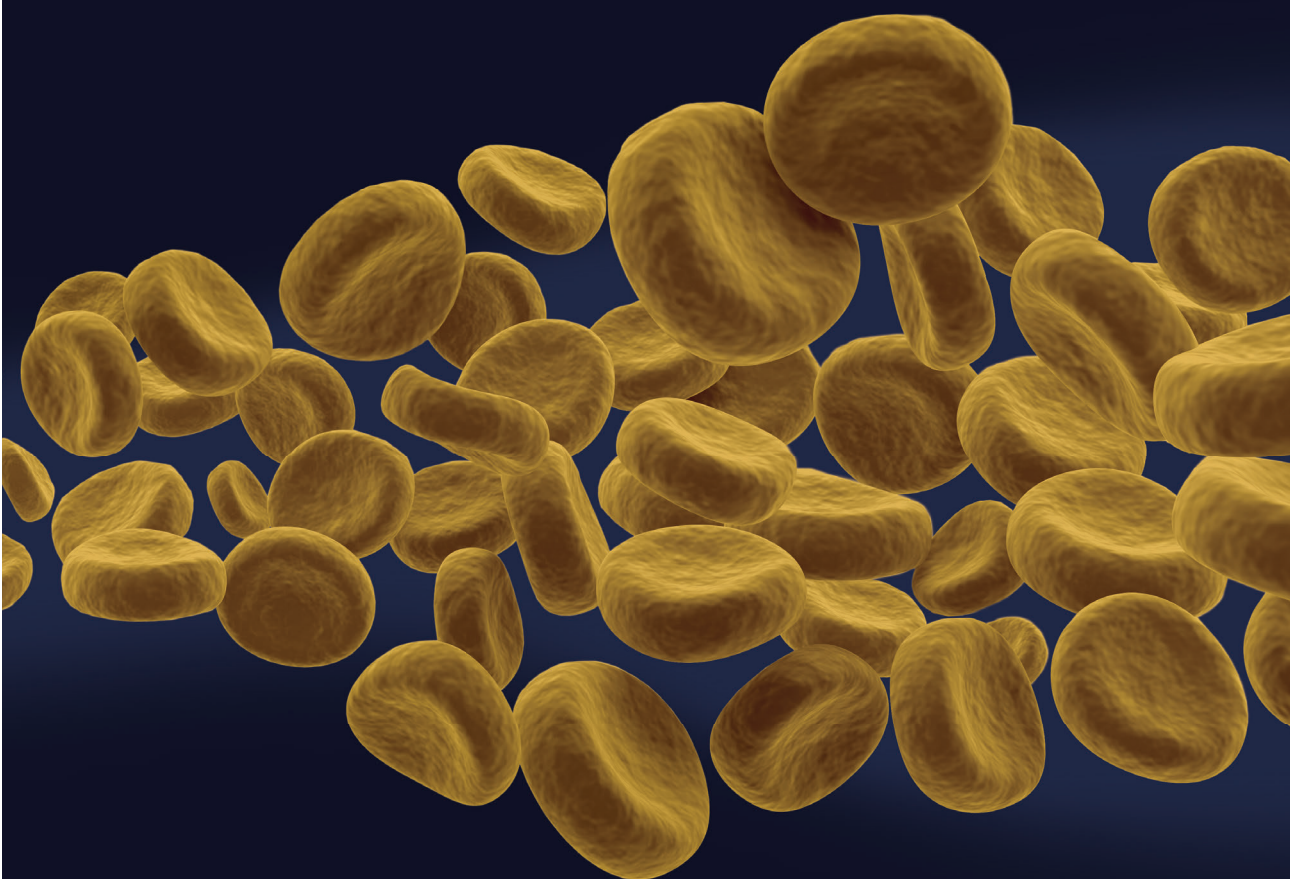
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# Part 1 - Overview







**General Introduction**



## General introduction

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 destroyed due to maternal IgG red blood cell alloantibodies that are transported across the placenta. The process of destruction of foetal red blood cells is named haemolysis.<sup>1,2</sup> The effects of maternal alloimmunisation to foetal red blood cell antigens, range from anaemia and hydrops in the foetus, to hyperbilirubinaemia and kernicterus in the newborn (Figure 1).<sup>2</sup>

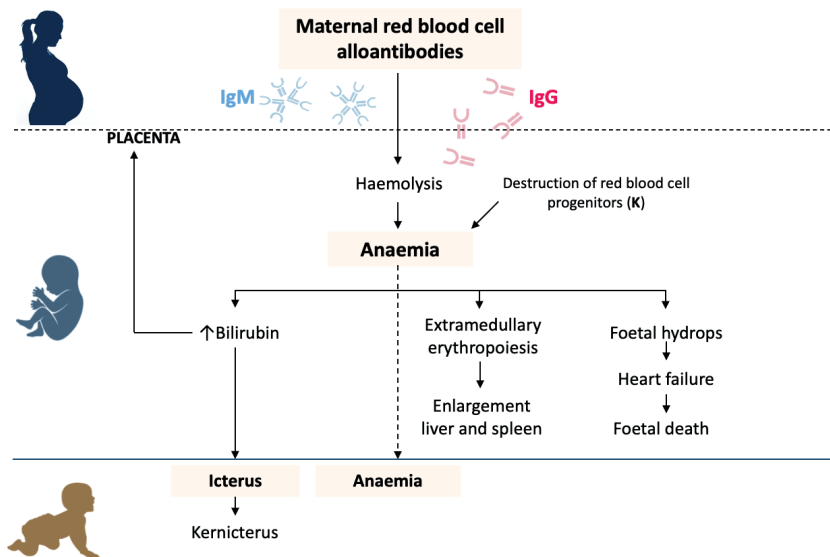


**Figure 1.** Pathogenesis of haemolytic disease of the foetus and newborn in the mother, foetus and newborn child. Adapted from De Haas, et al. *Vox Sang* 2015.<sup>1</sup>

## Historic overview

The symptoms of HDFN were first described by a French midwife named Louise Bourgeois in 1609. She described the birth and death of a twin pair: one baby was very swollen (hydropic) and died shortly after birth, the other, initially in good condition, developed jaundice and neurological symptoms (kernicterus) and died three days later.<sup>3</sup> In 1932, paediatric haematologist Dr. Louis Diamond identified these two conditions, hydrops foetalis and kernicterus, as two aspects of the same condition.<sup>4</sup> The first to hypothesise the antibody-related pathogenesis of HDFN, was pathologist Dr. Ruth Darrow in 1938. Following the loss of Darrow's third child to this disease, she correctly hypothesised that HDFN was caused by

destruction of red blood cells due to an incompatibility of maternal and foetal red blood cells and formation of antibodies in the mother's blood.<sup>5</sup> The nature of these antibodies was further clarified in 1940 by Dr. Karl Landsteiner, Dr. Alexander Wiener and Dr. Philip Levine, as the Rhesus (Rh) blood group system was discovered and the RhD antigen was identified.<sup>6,7</sup>

The most successful step in antenatal management of HDFN was prevention by the introduction of RhD immunoprophylaxis (RhIg) in 1969. Before immunoprophylaxis became available, HDFN affected 1% of all newborn children worldwide and the mortality rate in affected fetuses was up to 50%.<sup>8</sup> Besides prevention, a corner stone of antenatal management is early identification of pregnancies at risk. Since the 1960s, RhD-negative women are routinely screened for the presence of alloantibodies in the last trimester of pregnancy in the Netherlands. Since 1998, all pregnant women are routinely screened for antibodies in the first trimester, which highly contributed to a drastic decline in the occurrence of hydrops from 39% before 1998, to 15% afterwards.<sup>9</sup>

Monitoring of pregnancies at risk was first done in the 1950s by taking samples of the amniotic fluid and measuring the haemoglobin breakdown products (iron and urobilinogen), the so-called Liley index.<sup>10</sup> From the late 1990s onwards, the non-invasive assessment of the velocity of the blood flow in the middle cerebral artery by Doppler ultrasound has become standard of practice to assess foetal anaemia.<sup>11</sup>

For a long time, induced (preterm) labour of the foetus before it was too severely affected, was the only antenatal treatment option after identification of foetal anaemia. This changed in 1963, when Dr. Albert Liley introduced the procedure of intrauterine blood transfusion (IUT).<sup>12</sup> The complication risk of this procedure was unfortunately extensive after its first introduction, as the first IUTs were X-ray guided transfusions into the foetal peritoneum. Outcomes improved with more experience and the introduction of an ultrasound guided intravascular approach in the 1980s, into the umbilical vein.<sup>13</sup> Another antenatal treatment option is administration of intravenous immunoglobulins (IVIg). IVIg treatment seems to have a beneficial effect to postpone early IUTs in high-risk pregnancies, i.e. pregnancies of alloimmunised women with a history of severe haemolytic disease.<sup>14</sup>

Postnatal care revolves around the treatment of hyperbilirubinaemia by intensive phototherapy and exchange transfusions. Exchange transfusions were first performed for this cause in 1946 by Dr. Harry Wallerstein.<sup>15</sup> Exchange transfusions lower the serum bilirubin level and remove the antibody-coated neonatal red blood cells and circulating maternal antibodies to reduce further red blood cell destruction. Approximately 85% of the neonatal blood is replaced by irradiated donor

blood, which has the additional benefit of directly treating anaemia.<sup>16,17</sup> Exchange transfusion is an invasive procedure and although current mortality rates are less than 0.3% in term children, morbidity rates are still high (up to 24%).<sup>18</sup> Phototherapy, as a non-invasive alternative, has rapidly replaced exchange transfusions as standard of care for hyperbilirubinaemia after it was first introduced in 1958. It was discovered after observations of a nurse at a neonatal care unit in England, that children exposed to sunshine showed improvement of their jaundice.<sup>19</sup>

## Pathophysiology

Maternal alloimmunisation due to RhD and K (Kell blood group system) antigens is now known as the most common cause of severe HDFN, but varying degrees of alloimmunisation can be triggered by more than 50 different red blood cell antigens.<sup>21</sup> The clinical relevance of alloantibodies in pregnancy depends on the class of antibodies that are produced (only IgG antibodies are transported across the placenta), the presence of the specific antigen against which the alloantibodies are directed on the foetal red blood cells, and the level of expression of the specific antigen on the foetal red blood cells, as some red blood cell antigens are hardly expressed before birth.<sup>22</sup> In general, severe HDFN is most frequently caused by antibodies directed against RhD, K, or Rhc antigens and rarely by antibodies directed against other red blood cell antigens such as RhE, the Jk-antigens of the Kidd antigen system, or Fy-antigens of the Duffy antigen system.<sup>1</sup>

RhD and K-mediated HDFN are known to have a different pathophysiology and clinical course. In K alloimmunisation, even low antibody titres in pregnancy are associated with severe foetal anaemia that usually occurs more early in pregnancy compared to HDFN caused by RhD alloimmunisation. Overall, K alloimmunisation accounts for a higher need for IUTs and in general more IUTs per pregnancy.<sup>23</sup> K antigens appear on erythroid progenitor cells early in erythropoiesis,<sup>24</sup> and erythroid suppression seems to be the predominant mechanism in producing foetal anaemia, rather than haemolysis.<sup>25-27</sup> Although children affected by K alloimmunisation require overall less phototherapy and less exchange transfusions compared to RhD alloimmunisation, there is in both RhD and K alloimmunisation a similarly high degree of neonatal anaemia and transfusion dependency after birth.<sup>28</sup>

## **Aim and outline of this thesis**

Prevention and therapy of HDFN is generally considered a success story in perinatal medicine. In a relatively short time span, the pathophysiology of HDFN was unravelled, effective prevention programs were implemented worldwide, and successful antenatal and postnatal treatment strategies in experienced centres further minimised the risk of morbidity and mortality. Nonetheless, various aspects remain to be elucidated and there is still room to optimise both the antenatal and postnatal management and improve the short and long-term outcomes of this disease.

This thesis aims to add to the knowledge on the use and outcome of current therapy options in HDFN. An overview of the current neonatal management of HDFN is provided and the current standard procedures as exchange transfusions and top-up red blood cell transfusions and associated complications are thoroughly evaluated, as well as long-term outcomes after intrauterine transfusions (IUTs). This thesis also aims to set a base for further individualisation of treatment, in which a better selection of high-risk and low-risk cases should lead to a minimisation of late interventions. With this knowledge, this thesis strives to further contribute to successful management of HDFN.

## Outline

### **PART ONE      OVERVIEW**

General introduction

Chapter 1      Review on the available literature on neonatal management and outcome in HDFN.

### **PART TWO      PREDICTORS OF SEVERE DISEASE**

Chapter 2      Cohort study examining the use of foetal bilirubin as predictor of exchange transfusion.

Chapter 3      Cohort study on the suppressive effect of intrauterine transfusions on compensatory erythropoiesis.

### **PART THREE      NEONATAL MANAGEMENT AND COMPLICATIONS**

Chapter 4      Cohort study evaluating the incidence, associated risks and outcome of exchange transfusions over the last 20 years.

Chapter 5      Cohort study on the prediction of anaemia and transfusion dependency in the first three months after birth.

Chapter 6      Randomised controlled trial on the use of EPO to reduce postnatal transfusions in neonates with red blood cell alloimmunisation treated with intrauterine transfusions (protocol).

Chapter 7      Cohort study examining the association of necrotising enterocolitis with haemolytic disease of the newborn.

### **PART FOUR      LONG-TERM OUTCOME**

Chapter 8      Questionnaire cohort study evaluating school performance and behavioural functioning in children after intrauterine transfusions.

### **PART FIVE      SUMMARY AND DISCUSSION**

Summary

Nederlandse samenvatting

General discussion and future perspectives

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