Neonatal management and outcome in red cell alloimmunization

Smits-Wintjens, V.E.H.J.

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General introduction and outline of the thesis

Introduction

Hemolytic disease of the fetus and newborn (HDFN) due to red cell alloimmunization has been a fascinating clinical picture for many centuries. The first report of a condition called hydrops fetalis dates back to 1609,[1,2] when a French midwife described the delivery of twins. The first twin was hydropic and stillborn and the second suffered from jaundice and subsequently died of kernicterus. These two conditions were not linked until 1932, when Diamond et al. described that hydrops and kernicterus were manifestations of the same disease, which they called erythroblastosis fetalis.[3] However, the exact cause was still unknown. Since 1940, the analyses of Landsteiner and Wiener contributed largely to a better understanding of the pathogenesis of HDFN.[4-7] In their studies with rhesus monkeys Landsteiner and Wiener observed that agglutination of human red blood cells occurred in the presence of rhesus monkey red cell antiserum, whereas subjects who lacked the antigen on their red cells did not show agglutination.[4,7] The authors called this antigen 'Rhesus' (Rh) and consequently the Rh-blood group system was born. Since then it has become clear that the most common cause of severe HDFN is 'Rhesus disease', resulting from maternal immunization to the Rhesus D (Rh D) antigen.[8] However, more than 50 other red cell antigens associated with hemolytic disease have been described. Not only anti-Rh D, but also anti-Rh c and anti-Kell antibodies are associated with severe fetal and neonatal disease.[9]

Untreated HDFN is a major cause of perinatal mortality. In HDFN due to red cell alloimmunization, maternal immunoglobulin (IgG) antibodies directed against fetal red blood cells, pass the placenta into the fetal circulation and cause destruction of fetal red cells. The resulting progressive fetal anemia will then lead to fetal hydrops and perinatal death.[10]

During the last few decades prenatal care for patients with red cell alloimmunization has improved significantly. The introduction of Rh D prophylaxis in the late 1960s,[11,12] the use of Doppler ultrasound to detect fetal anemia since the early 1970s[13] and treatment with intrauterine intravascular red cell transfusions (IUT) since the 1980s[14-16] have led to a remarkable reduction in perinatal mortality. Before the introduction of Rh D prophylaxis and IUTs, perinatal mortality was approximately 50% and the rate of perinatal morbidity was extremely high.[1,17] The current most successful treatment, the use of IUTs, contributed largely to perinatal survival rates exceeding 95% in experienced centers.[10,18] As a result of improving prenatal care strategies and consequently increased perinatal survival, attention is now shifting towards postnatal short-term and long-term management and morbidity.

Neonatal red cell alloimmunization may lead to excessive hyperbilirubinemia and permanent brain damage due to kernicterus. Postnatal management is based mainly on the treatment of hyperbilirubinemia and consists of intensive phototherapy and exchange

transfusion (ET).[18] Despite improvement in neonatal intensive care, ET remains a high risk invasive procedure requiring the use of central lines and is associated with a significant rate of adverse reactions.[19-26] Neonatal treatment with intravenous immunoglobulins (IVIg) has been suggested and used as an alternative therapy for ET.[27] In a few small randomized controlled trials IVIg reduced the need for ET and duration of phototherapy. However, these studies were restricted by several important methodological limitations.[28-31] In 2002 a Cochrane review suggested that more well-designed trials were needed before routine use of IVIg could be recommended for treatment of HDN due to red cell alloimmunization.[32]

Postnatal management also consists of treatment of early and late anemia using top-up red blood cell transfusions.[33] Several risk factors for neonatal anemia secondary to red cell alloimmunization have been reported, including IUT[34], severity of HDN[35,36], type of alloimmunization (including Kell versus Rh D)[37] and the use of ET.[18,38] However, only a limited number of studies (mostly case reports) have been published on differences in type of alloimmunization related to severity of neonatal anemia.[37,39-41] In addition, the protective role of ET for neonatal anemia has only been demonstrated in one small study.[38] Therefore, further research on anemia secondary to red cell alloimmunization is needed.

In the past, various other postnatal complications in neonatal red cell alloimmunization have been reported, including cholestatic liver disease and thrombocytopenia. The etiology of cholestasis in neonates with HDN due to red cell alloimmunization has been attributed to iron overload due to IUT.[42-45] However, data on incidence, potential risk factors, neonatal management and outcome of cholestasis in red cell alloimmunization is scarce. Simultaneously, only a few small studies have been published on incidence and severity of thrombocytopenia in neonates with red cell alloimmunization.[36,46-48] Therefore, more studies are needed to investigate these and other associated complications of neonatal red cell alloimmunization.

As perinatal survival improves, attention is shifting towards long-term outcome in survivors. One of the concerns of the successful use of IUTs is that a decrease in perinatal mortality may lead to an increase in children with long-term handicaps. Moreover, not much is known about the relation between the severity of fetal anemia and long-term neurodevelopmental outcome.[18] To date, only a few studies with small patient numbers have reported long-term neurodevelopmental outcome after IUT.[49-56] Further research on this topic is needed to determine incidence of and risk factors for adverse neurodevelopmental outcome after IUT.

The aim of this thesis was to investigate various management options and to describe complications and outcome of neonatal red cell alloimmune hemolytic disease.

Outline of the thesis

During this study period several study projects on management, complications and outcome in hemolytic disease of the newborn (HDN) due to red cell alloimmunization were performed, including the **L**eiden's **IVI**g trial in Rhesus disease of the **N**eonate (**LIVIN** study) and the **LO**ng-**T**erm follow-up after intra**U**terine transfusion**S** (**LOTUS**) study. The LIVIN study is a randomized controlled trial (RCT) designed in collaboration with Sanquin Blood Bank (Southwest Region, Amsterdam) to determine whether the prophylactic use of IVIg reduces the need for ET in neonates with Rh D or c hemolytic disease. The LOTUS study is a large national cohort study designed in close collaboration with the Department of Obstetrics and the Department of ImmunoHematology and Blood Transfusion of the Leiden University Medical Center (LUMC). One of the aims of the LOTUS study was to evaluate the long-term neurodevelopmental outcome of children treated with IUT. The aims and outcomes of these and other studies are described in the following chapters:

Chapter 2
Review of the literature on HDN due to red cell alloimmunization. This review focuses on postnatal management, associated morbidity and long-term outcome.

Chapter 3
Randomized controlled trial on the use of IVIg in neonates with Rhesus HDN (LIVIN study), investigating the effect of IVIg on number of ETs.

Chapter 4
Case report describing a term neonate with Rhesus hemolytic disease treated with ET and developing a rare but severe cerebral infection after umbilical cord catheterization.

Chapter 5
Study on morbidity associated with ETs in neonatal red cell alloimmune hemolytic disease.

Chapter 6
Study on cholestasis in neonates with red cell alloimmune hemolytic disease, describing incidence, risk factors and outcome.

Chapter 7
Study on thrombocytopenia at birth in neonates with red cell alloimmune hemolytic disease, focusing on incidence and severity of and risk factors for thrombocytopenia at birth.

Chapter 8
Study on top-up red blood cell transfusions in neonates with Rhesus hemolytic disease in relation to ETs.

Chapter 9
Study on neonates with Kell hemolytic disease, focusing on ETs and top-up red blood cell transfusions.

Chapter 10
Study on long-term neurodevelopmental outcome after IUT for fetal alloimmune anemia (LOTUS study), to determine the incidence of and risk factors for neurodevelopmental impairment (NDI).

Chapter 11
General discussion and future perspectives

Chapter 12
Summary

Chapter 13
Samenvatting

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