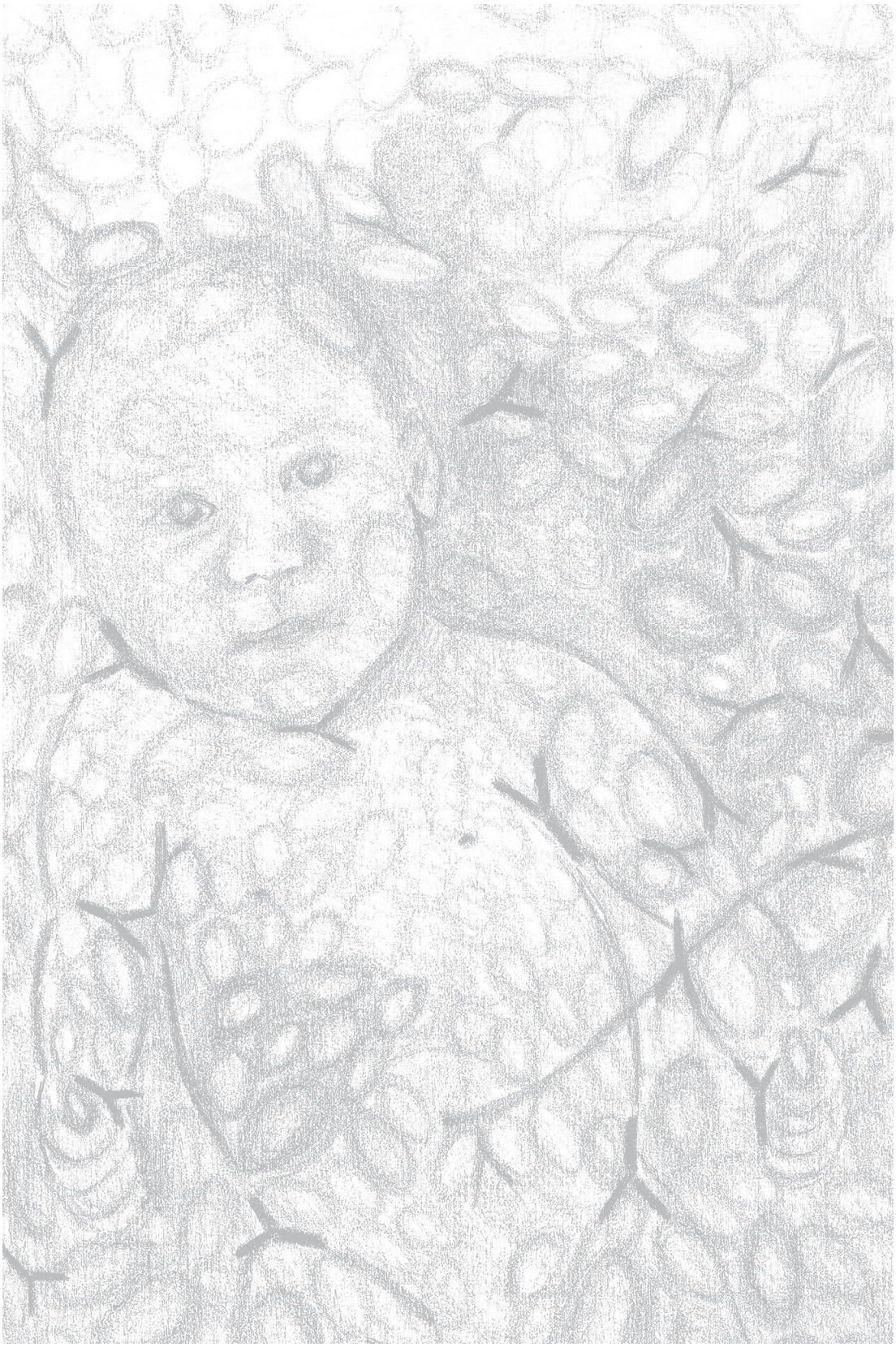

Chapter 1

General introduction

General introduction

Pathophysiology

Hemolytic disease of the fetus and newborn (HDFN), in earlier times known as erythroblastosis fetalis, is a condition in which fetal and neonatal red cells are destructed by the action of IgG antibodies derived from the mother by placental transfer. Maternal alloimmunization usually occurs after fetal-maternal hemorrhage at the time of delivery or during pregnancy when fetal red cells which express paternally derived antigens enter the maternal circulation.[1] In contrast to fetal and neonatal alloimmune thrombocytopenia, first pregnancies in HDFN are usually not affected because fetomaternal hemorrhage is too small or too late to cause formation of IgG antibodies.[1,2] Maternal immunization may also result from a blood transfusion and partly for that reason primigravida can still be affected.[3]

Over 50 red blood cell antigens can cause HDFN, however only Rh D, Kell (K1) and Rh c alloimmunization are frequently associated with severe fetal disease.[4] When fetal disease is left untreated, this can lead to progressive fetal anemia, fetal hydrops and fetal death. Fetal hydrops consists of abnormal fluid accumulation in fetal compartments, including ascites, pleural effusion, pericardial effusion, and skin edema. It is assumed that immune fetal hydrops results from congestive heart failure due to severe anemia.[5-7]

After birth, placental transfer of antibodies stops, but already derived antibodies can remain in the circulation for several months. As a consequence, hemolysis continues leading to neonatal hyperbilirubinemia and anemia which can be present up to three months of age.[8] Hyperbilirubinemia is usually not present in the fetal period because fetal bilirubin is transferred through the placenta and excreted by the mother. Neonatal hyperbilirubinemia arises from a transient deficiency of conjugation in the liver (exacerbated in premature neonates) and increased red cell turnover.[9]

HDFN is a complex disorder and disease severity seems to depend on many factors. These factors include: concentration, specificity, subclass, and glycosylation of antibodies; density, structure, and tissue distribution of antigens; efficiency of placental transport; functional maturity of the fetal spleen; macrophage Fc receptor function and the presence of HLA-related inhibitory antibodies.[10] In Kell HDFN for example, hyperbilirubinemia is usually not severe because anti-Kell antibodies cause suppression of erythropoiesis rather than hemolysis of erythrocytes.[11-13]

Prevalence

The exact prevalence of HDFN is difficult to determine because it depends on how HDFN is defined and the population in which it is measured. Reported prevalence of severe HDFN

varies from 3/100.000 to 80/100.000 pregnancies in developed countries.[14] In low income countries, prevalence of Rh negativity is lower than in North America and Europe. However, from data from three low income countries it is estimates that the prevalence of Rh HDFN varies from around 200/100.000 to around 340/100.000 births. In those countries there is a lack of Rh D prophylaxis leading to more neonates at risk.[15]

Prevention

Primary prevention of HDFN consists of extended matching of red blood cell (RBC) transfusions and the administration of Rh D immunoprophylaxis. In addition to ABO and Rh D matching of RBC transfusions, Dutch guidelines recommend matching for K, Rh c and Rh E for women below 45 years of age.[16] However, in many other countries this extensive matching is not routine practice. Rh D immunoprophylaxis has been licensed in Europe and North America since 1968. As a consequence, Rh D immunization rate decreased from 13.2% to 0.14% per Rh D positive pregnancy in Rh D negative mothers.[17] Nevertheless, maternal sensitization from fetomaternal hemorrhages will continue due to insufficient administration of Rh D immunoprophylaxis and the unavailability of immunoprophylaxis to prevent sensitization to non-Rh D antigens.

Antenatal management

Fetuses at risk are identified by maternal antibody screening and titration, determination of paternal antigen status, and determination of fetal antigen status.[18] The latter can be done by amniocentesis or noninvasively using free fetal DNA in maternal plasma. This noninvasive fetal blood group typing was first reported by Lo et al. in 1998.[19] Fetuses at risk were used to be monitored by amniotic fluid bilirubin measurements and cordocentesis to determine fetal anemia. However, currently noninvasive detection of fetal anemia by Doppler assessments of peak systolic velocity in the fetal middle cerebral artery is used predominantly.[20-22]

Treatment of fetal anemia by intrauterine intraperitoneal RBC transfusion was introduced in 1963.[23] In the 1980s intravascular transfusion via umbilical vessels became practice.[24,25] With improvement of this intravascular technique, nowadays overall perinatal survival rates in experienced centers vary between 89% and 92%.[26,27] Other proposed antenatal treatment options include maternal or fetal administration of intravenous immunoglobulin and maternal administration of phenobarbital.[29-32] However, further studies are needed to elucidate the role of those treatments.

Neonatal management

After birth, diagnosis of HDFN can be confirmed by blood group and Rh typing, measuring antibodies and bilirubin, and performing direct antibody (Coombs') test.[33]

Neonatal treatment of HDFN mainly consists of treatment of hyperbilirubinemia with phototherapy and exchange transfusion and correction of anemia. Severe (unconjugated) hyperbilirubinemia can lead to acute bilirubin encephalopathy and chronic bilirubin encephalopathy, also known as kernicterus.[34] Phototherapy, which was introduced in the 1970s, can prevent severe hyperbilirubinemia by photo-oxidation of bilirubin in the skin which converts it to a water-soluble substance. In the late 1940s treatment of neonatal hyperbilirubinemia with exchange transfusion (ET) was introduced.[35] ET not only removes bilirubin from the circulation to prevent kernicterus, but also maternal antibodies limiting further hemolysis. In addition, ET also corrects the associated anemia. ET is a high-risk invasive procedure and several alternative treatment options have been studied to reduce the need for ET, including intravenous immunoglobulin (IVIg), albumin, phenobarbarbital and metalloporphyrins. The use of the latter three options is not recommended since there is not sufficient evidence.[34] A Cochrane review on the use of IVIg in neonates with HDFN in 2002 concluded that IVIg was effective in reducing ET requirements. However, authors commented that evidence was limited due to small size and low quality of the studies and that routine use cannot be recommended.[34,36] Despite this advice, the guidelines of the American Academy of Pediatrics of 2004 advocate the routine use of IVIg in neonates with HDFN and consequently the use of it became widespread.[33,34]

Top-up transfusions, also known as simple or RBC transfusions, are used to treat anemia up to three months of age. In addition, several medicaments are used to stimulate erythropoiesis. These treatment options and the management of other hematological complications of HDFN are reviewed in this thesis.

Outline of the thesis

The Leiden University Medical Center (LUMC) is a tertiary center and the national referral center for intrauterine treatment of pregnancies complicated by red cell alloimmunization. Yearly around 35 neonates with HDFN due to red cell alloimmunization are admitted to the neonatal intensive care unit in the LUMC.

The aim of this thesis is to study the management and hematological outcome in neonates with HDFN.

The following chapters describe the objectives in more detail:

Chapter 2	Literature review on hematological morbidity and treatment options in HDFN due to red cell alloimmunization.
	Part 1: Exchange transfusions
Chapter 3	Study on the influence of a more restrictive ET guideline on the top-up transfusion requirements in neonates with Rh HDFN.
Chapter 4	Study on the morbidity associated with ET for red cell alloimmune hemolytic disease.
	Part 2: Intravenous immunoglobulin
Chapter 5	Randomized controlled trial on the use of IVIg in neonates with Rh HDFN (LIVIN study) investigating the effect of IVIg on the number of ETs.
Chapter 6	Cochrane systematic review on the use of IVIg in neonates with alloimmune hemolytic disease.
	Part 3: Alloimmunizations other than Rh D
Chapter 7	Study on the postnatal management and outcome in neonates with Kell hemolytic disease compared to Rh D hemolytic disease.
Chapter 8	Study on the postnatal management and outcome in neonates with Rh c hemolytic disease compared to Rh D hemolytic disease.

Part 4: Associated hematological morbidity

Chapter 9	Study on the incidence and severity of and risk factors for thrombocytopenia at birth in neonates with HDFN due to red cell alloimmunization.
Chapter 10	Study on the incidence and severity of and risk factors for cholestasis in neonates with HDFN due to red blood cell alloimmunization.
Chapter 11	Study on iron status during first three months of life in neonates with HDFN due to red cell alloimmunization.
Chapter 12	Summary and general discussion concerning the results of these studies.
Chapter 13	Future perspectives and proposals for future research.

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