Hemolytic disease of the fetus and newborn: awareness precedes change

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PART I

OVERVIEW

General Introduction And Scope Of This Thesis

HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

Hemolytic disease of the fetus and newborn (HDFN) is a potentially life-threatening disease caused by the destruction of fetal and neonatal red blood cells (RBC) due to maternal alloantibodies directed against paternally inherited blood group antigens (**Figure 1**). In HDFN, maternal immunoglobin G (IgG) is actively transported across the placenta by the neonatal Fc receptor (FcRn). The most common alloantibodies in HDFN are directed against the Rhesus (Rh) D, Kell (K1) antigen, Rhc and RhE antigens. However, other, more rare alloantibodies directed against blood group antigens such as Duffy (Fy^a and Fy^b), Kidd (Jk^a and Jk^b), and M, may also induce HDFN. Once present in the fetal circulation, these alloantibodies may bind to and destroy fetal RBCs leading to fetal anemia. In case of Kell-mediated HDFN, fetal erythropoiesis itself is inhibited. If left untreated, fetal anemia can progress into hydrops fetalis ultimately leading to fetal death.

After delivery, circulating alloantibodies cause a continued destruction of neonatal RBCs and induce severe hyperbilirubinemia. If left untreated, severe hyperbilirubinemia may cause permanent brain injury known as Kernicterus Spectrum Disorder. Throughout the first three months of life, anemia may develop owing to continued hemolysis and an inhibition of erythropoiesis.

The disease's pathophysiological mechanism and subsequent disease severity is multifactorial, depending for instance on the quantity of alloantibodies, fetal Fc-gamma receptor polymorphisms, IgG subclasses, IgG-Fc-glycosylation profiles, ability of the fetus to increase its compensatory erythropoiesis, and other (unknown) factors.

This chapter provides an introduction into the disease's pathophysiology, history, the current screening and prevention of alloimmunization, and the antenatal and postnatal management of pregnancies and neonates affected by HDFN, followed by a contextual framework for this thesis.

HISTORY IN THE NETHERLANDS

Initiation of blood transfusion services

In 1925, the first blood transfusion in the Netherlands was administered[1] and only five years later, the first blood transfusion service was established by physician Dr. Henri van Dijk in the Diaconessenhuis in Rotterdam in 1930.[1] The subsequent surge in blood transfusion services across the country in the following years called for a more centralized approach. In 1939 the 'Centrale Medische Bloedtransfusie

Commissie' of the Dutch Red Cross and the military medical service of the Dutch Royal Army established two 'conserveer-inrichtingen', one in Amsterdam and one in Rotterdam.[1] Four years later, the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB) led by Dr. Jan Spaander was established to centrally coordinate numerous blood banks (**Figure 2**).[1]

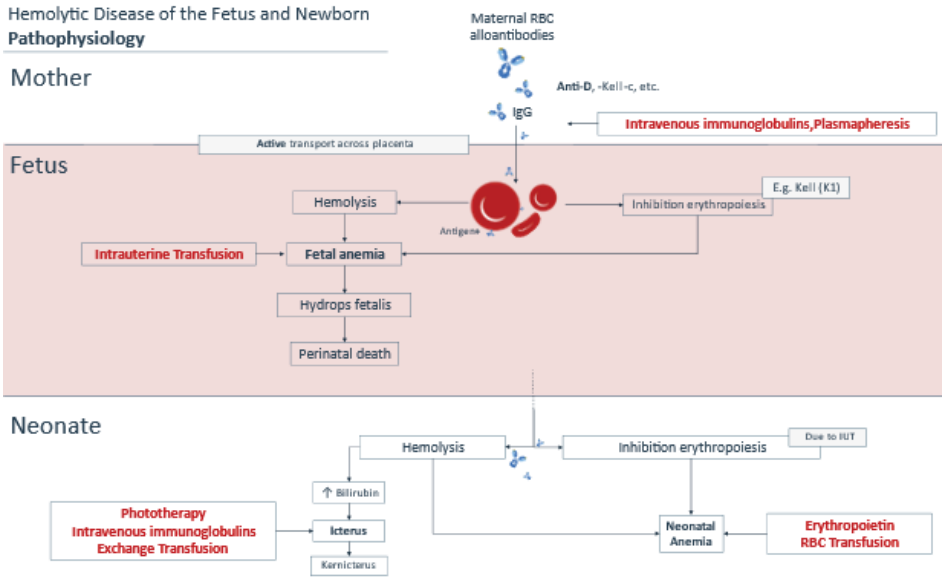

Figure 1: Pathophysiology of HDFN and treatment options.

With the discovery of the Rh (previously known as Rhesus) blood group in 1940 and the subsequent improved understanding of the disease, the CLB, obstetricians and pediatricians from across the country met in June 1946 in Leiden at the Institute for Preventative Medicine for the meeting '*vergadering van belangstellenden in het Rhesusvraagstuk*' (In English this would be: "meeting for those interested in the Rhesus issue).[2] At that time, HDFN research was conducted independently across various hospitals and institutions. This meeting established the groundwork for nationwide collaborations across different fields:

> *"Samenwerking tusschen verschillende groepen onderzoekers is noodzakelijk, liefst in teamverband. Onder centrale leiding, eventueel naar Engelsch voorbeeld, waardoor goed opgezet onderzoek mogelijk is en waar met inschakeling van den bloedtransfusiedienst ook organisatorisch en coördineerend veel bereikt kan worden." Prof. Dr. Henk Veeneklaas, June 15, 1946.*[2]

In English this quote would be: "*Collaboration between different groups of researchers is essential, preferably as a team. Under central leadership, possibly following the English model, well-structured research becomes feasible, and with the involvement of the blood transfusion services, much can be achieved both organizationally and in terms of coordination.*"

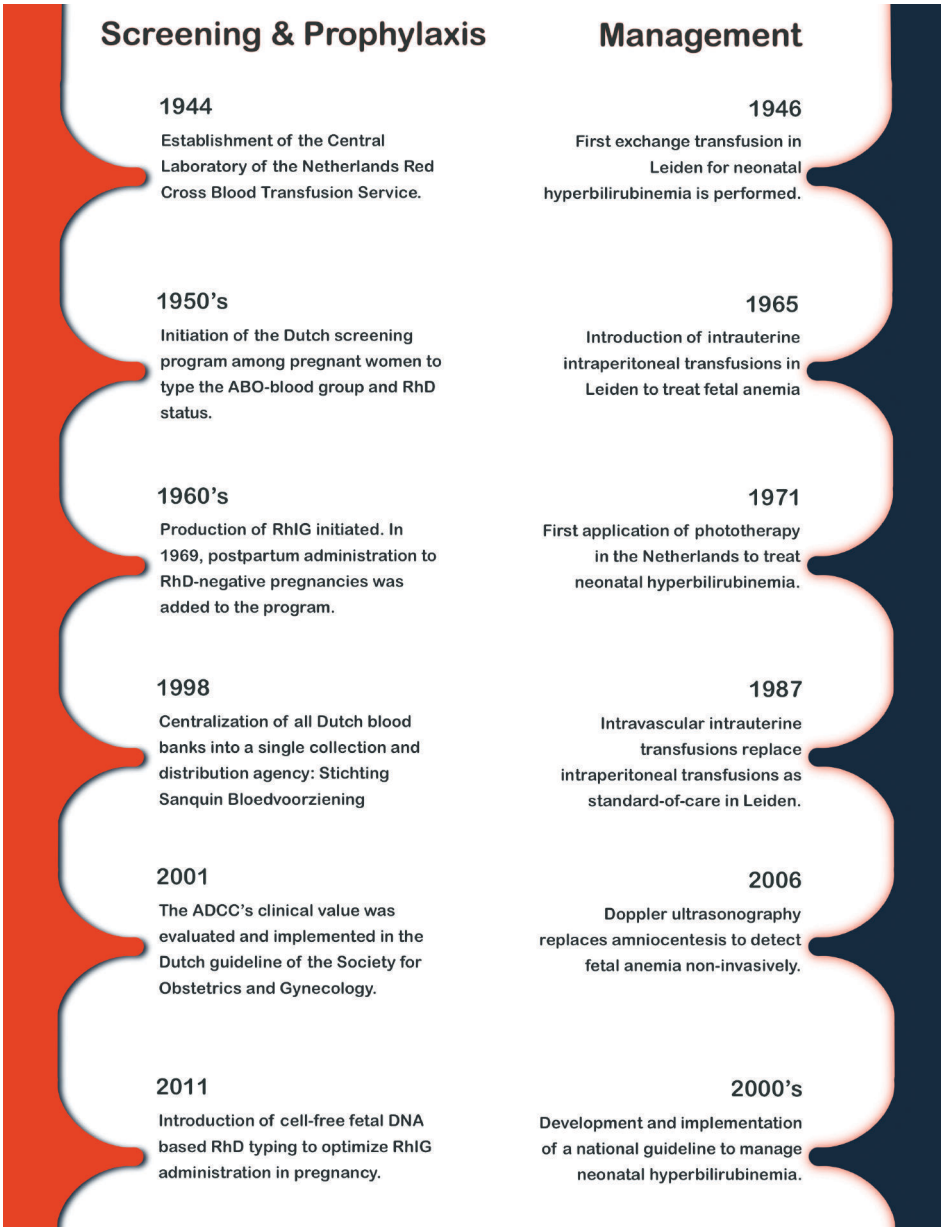

Figure 2: Key historical events in the Netherlands in the management of HDFN.

The Dutch screening and prophylaxis program

Shortly after this meeting, in the 1950's, the Dutch screening program was initiated. At first, the screening program among pregnant women was to detect syphilis and to determine the ABO-blood group, whereas in 1952, RhD typing was added.[3] Studies on the successful prevention of RhD sensitization using anti-D antibody preparations sparked worldwide initiatives to establish methods to prevent RhD sensitization. A working party consisting of Dr. Els Borst-Eilers, Dr. Christina van der Weerdt, Prof. Dr. Gerrit-Jan Kloosterman and Dr. Chris Dudok de Wit started a campaign in 1964 to prevent RhD-alloimmunization and one year later the first Dutch batch of RhD immunoprophylaxis (RhIG) was produced by Dr. Herman Krijnen at the CLB.[4] In 1969, postpartum administration of RhIG in the first pregnancy to RhD-negative pregnant women that delivered a RhD-positive and ABO-compatible child was added to the screening and prophylaxis program. RhIG was then acquired from donations from 150 immunized volunteers, of whom 141 were immunized intentionally (with informed consent) for donation purposes.[4] A year later in June 1970, the RhIG supply was sufficient to also provide postpartum prophylaxis in the second pregnancy and restrictions on ABO-compatibility were lifted, and in 1971 the RhIG supply was sufficient to lift all restrictions and provide prophylaxis to all RhD-negative women who gave birth to a RhD-positive child regardless of gravidity or parity.[4] In this period, Prof. Dr. Paul Engelfriet and Drs. Marijke Overbeeke from the immunohematology laboratory of Sanquin invested time and efforts to educate the field of laboratory medicine to perform necessary testing. Back then, the Netherlands accounted for a total of 110 separate blood transfusion services that were centralized into 22 regional and independent blood banks.[1] In 1998, all 22 Dutch blood banks and the CLB were merged into a single-collection and distribution agency: Sanquin Blood Supply Foundation. This national centralized blood bank organization continued their work under the banner of the pelican, a symbol for selflessness and sacrifice first adopted by the first Dutch blood bank in Rotterdam in 1930.[1] In that same year, 1998, prenatal RhIG administration in gestational week 30 was introduced and given to RhD-negative pregnancies who had not yet delivered a liveborn child. In 2008, this restriction was lifted and all RhD-negative pregnant women received RhIG in gestational week 30. Then, in 2011, the work of Prof. Dr. Ellen van der Schoot, led to the introduction of cell-free fetal DNA-based RhD typing in the screening program, which provided the opportunity to target antenatal RhIG administration specifically to RhD-negative women pregnant of a RhD-positive fetus, limiting unnecessary use and thus wastage of a limited supply of RhIG.[5] Taken together, these advancements have significantly lowered the rate of new immunizations among RhD-negative pregnant women to now approximately 0.31%.[6-8] However, the fractioning of anti-RhD plasma by Sanquin Blood Supply was stopped in 2020 leading to the discontinuation of anti-RhD plasma collection from donors. As a

result, the Netherlands and many other regions of the world are no longer self-sufficient and now heavily rely on American donors to meet their anti-RhD plasma needs. This growing dependency highlights a critical vulnerability in global RhIG supply chains.

In early years, determining the risk of disease in sensitized RhD-negative pregnancies relied on alloantibody titers. However, discrepancies arose when some pregnancies showed high alloantibody titers but resulted in no or only mild disease. Therefore, in 1984, the Netherlands implemented the monocyte antibody-dependent cell-mediated cytotoxicity (ADCC) assay due to its better correlation with the severity of disease compared to the alloantibody titer alone.[9-11] The clinical value of the ADCC was further evaluated in 2001[12] and the results were put into practice in the national guideline of the Dutch Society for Obstetrics and Gynecology.[13]

Developments in managing pregnancies and neonates.

The improved understanding of HDFN that occurred after the 1940's also led to numerous developments in the management of affected pregnancies, fetuses and neonates. In 1946, the first exchange transfusion for severe neonatal hyperbilirubinemia was performed at the Leiden University Hospital, with the knowledge introduced by Prof. Dr. Henk Veeneklaas.[14] The introduction of exchange transfusions dramatically decreased mortality in affected neonates from approximately 60% to 22%.[15] However, severely affected pregnancies (i.e. with fetal anemia) remained untreatable, with high perinatal mortality rates. That was until 1965, when Prof. Dr. Jan Bennebroek Gravenhorst first traveled to New Zealand to learn from Prof. Dr. Liley how to perform intrauterine intraperitoneal transfusion[16] and then introduced this new technique at the Leiden University Hospital. Intraperitoneal transfusions resulted in increased survival rates among affected fetuses of up to 70% in the first years after its introduction (**Figure 3A**).[9] Intrauterine transfusions (IUT) at that time relied on visualizing the fetus by X-ray, along with water- and fat-soluble contrast mediums to outline the fetal gut and skin.[17] The use of real-time sonography to perform IUTs since 1978 further increased survival rates.[4] In 1987, Prof. Dr. Humphrey Kanhai introduced for a new and more effective technique using intravascular IUTs[18], which quickly replaced intraperitoneal transfusions as standard-of-care in the Netherlands.[19-21] However, the diagnosis of fetal anemia and the need for fetal transfusion still depended on serial amniocentesis to determine bilirubin levels in amniotic fluid.[22] A publication on Doppler ultrasonography by Mari et al. in 2000 introduced a promising non-invasive method to detect fetal anemia[23], and in 2006 the multicenter DIAMOND-study led by Prof. Dr. Dick Oepkes provided the evidence to globally replace amniocentesis by Doppler ultrasonography to detect fetal anemia.[24]

Significant advancements took place in the pediatric field alongside progress in the obstetrical field (**Figure 3B**). In 1968, Prof. Dr. Jan Ruys established the department of Neonatology at the Leiden University Hospital. At that time, the treatment of neonates with severe hyperbilirubinemia still depended upon invasive exchange transfusions, mostly owing to the lack of an alternative treatment option.[25] Discoveries on the effect of sunlight exposure on the jaundiced neonates sparked developments on non-invasive "artificial-light treatment"[26], now referred to as phototherapy. In the Netherlands, phototherapy was first introduced in 1971 and caused considerable decreases in exchange transfusion frequency.[27] Further improvements, such as the implementation of the national hyperbilirubinemia guideline, that was based on the guideline of the American Academy of Pediatrics published in 2004, further decreased exchange transfusion frequencies and improved outcomes in these affected neonates.

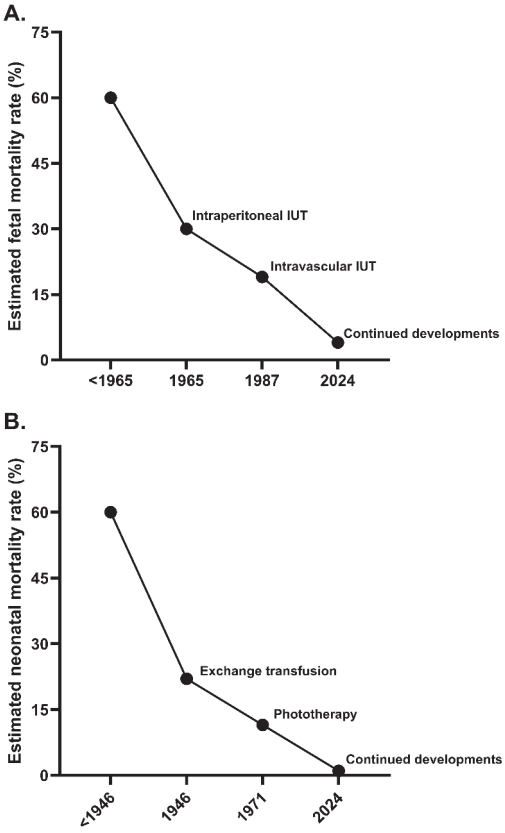

Figure 3: Estimated fetal (A) and neonatal (B) mortality rates in fetuses and neonates affected by HDFN throughout the decades based on developments that occurred.

With the quick adoption of international developments and through the national centralization of care at Sanquin Blood Supply Foundation and the Leiden University Medical Center and close collaboration between these organizations, the Netherlands proved to be a frontrunner in this field of fetal medicine. The Netherlands has been actively involved in international collaborations and through extensive efforts in research with more than 250 published papers on HDFN we have provided valuable input to advance our insights into the diagnosis, treatment and prevention of RBC sensitization in pregnancy.

GLOBAL CONTEXT

These numerous national developments took place within a broader global context. The origin of HDFN dates back to around 400 BC in Greece as described in Chapter 1. At that time, Hippocrates, the founder of modern medicine, first described a "*fetus carnosus*" now believed to have been hydrops fetalis.[25] Nearly 20 centuries later in 1609, a French midwife Louise Bourgeois reported another case with hydrops fetalis[28], and numerous written reports on similar cases followed in the centuries thereafter.[29] However, these symptoms remained poorly understood until Karl Landsteiner and his colleagues discovered and described the ABO (1900)[30] and Rh (Rhesus) blood group system (1940).[31] From that point forward, research in transfusion medicine, obstetrics and neonatology to prevent alloimmunization and manage pregnancies, fetuses and neonates with HDFN surged rapidly. Owing to the implementation of screening and prevention programs, also including preventive matching for RhD, K1 (Kell) and other Rh antigens upon the selection of RBC units for women with childbearing potential, the prevalence of alloimmunization in pregnancy in most high-income countries has dropped dramatically and HDFN is deemed a rare disease. Additionally, the few pregnancies, fetuses and neonates with HDFN managed in high-income countries generally have good outcomes.

Despite these advances that seemingly occurred on a global scale, there are wide disparities between high-income countries and many low- to middle-income countries. The lack of material needed to screen and type pregnant women, the lack of (affordable) polyclonal RhIG to prevent alloimmunization, and the lack of many treatment options affect large parts of the world such as South-East Asia, Middle- and South America, the Middle East and Africa. All in all, despite many great improvements, there is still much work to be done.

CURRENT DUTCH SCREENING, PREVENTION AND MANAGEMENT

Serological monitoring

In the Netherlands, women with clinically relevant alloantibodies, such as anti-RhD, anti-K1 (Kell), anti-Rhc and more rare types, such as anti-RhE, anti-Rhe, anti-Fy^a, and who are pregnant with a fetus that is positive for the implicated antigen undergo serological monitoring at regular intervals by determination of the alloantibody titer and for some of these antibodies the ADCC.[32] The antibody titer, as a measure for quantity, is determined through sequential dilution of maternal serum in an indirect antiglobulin test in tubes using fresh donor RBCs, positive for the implicated antigen. The highest titer is the dilution in which the indirect antiglobulin test is positive, reported as 1:1, 1:2, 1:4 and so forth.[32] The ADCC is solely performed in the Netherlands and is a measure for antibody-related hemolytic activity. The ADCC is done by assessing in-vitro monocyte-mediated hemolysis of Chromium-51 labelled RBCs, through incubation with undiluted maternal serum. The ADCC level is determined by the amount of Chromium-51 that is released through hemolysis that is expressed as a percentage reaching from <10% to a maximum of >80%. The higher the percentage, the more hemolysis may be expected.[32] Pregnancies that reach or exceed the predetermined cut-off values are regarded as at-risk for fetal anemia and are monitored at a local hospital and/or the LUMC. The aim is to timely refer for IUTs if necessary.

Antenatal management

Pregnancies at risk of developing severe HDFN are managed by timely detecting fetal anemia through weekly Doppler ultrasonography of the peak-systolic velocity of the middle cerebral artery[23,24] and assessments of secondary signs of anemia, followed by fetal blood sampling and an IUT with donor blood negative for the implicated antigen, if fetal anemia is present.[33] Early detection and treatment of fetal anemia prevents the development of hydrops fetalis, and ultimately, if left untreated, perinatal death.[25,33]

IUTs have significantly improved perinatal outcomes in fetuses with anemia, but these invasive procedures are associated with risks, especially in early gestations.[34] Intravenous immunoglobulin (IVIG) administration and plasmapheresis have therefore been proposed as treatments to delay the onset of fetal anemia in pregnancies with a history of severe HDFN, and bridge the gap towards later gestations.[35-38] However, data on the efficacy of IVIG, with or without plasmapheresis, to prevent or delay fetal anemia have shown a persisting high need for early IUTs.

Lastly, induction of preterm delivery (before 37 weeks of gestation) is widely accepted in high-risk pregnancies to limit the consequences of increasing IgG transport and, theoretically, limit postnatal hemolysis.[25] But, this strategy of preterm delivery has an associated trade-off, involving decreased fetal maturation and potentially less favorable short- and long-term outcomes.

Postnatal management

Postnatal treatment focuses on managing hyperbilirubinemia by intensive phototherapy, and if needed, exchange transfusions in order to prevent Kernicterus Spectrum Disorder.[25,39] Intensive phototherapy serves as the first-line treatment for hyperbilirubinemia, due to its effectiveness and low risk of adverse events. Exchange transfusions should be considered when serum bilirubin levels reach or exceed predetermined thresholds.[40] Additionally, intravenous immunoglobulins may be administered to restrict hyperbilirubinemia severity and delay or prevent an impending exchange transfusion.[40] However evidence on the effectiveness of IVIG in such situations is limited.[41]

Maternal alloantibodies remain in the infant's circulation for up to three months, leading to continued destruction of RBCs and late anemia of hemolytic disease. In addition, antenatal treatment with IUT may disrupt erythropoiesis (i.e. hyporegenerative anemia), further aggravating neonatal anemia.[25,42,43] In case of anemia, RBC transfusions may be considered to bridge the gap until the infants' erythropoiesis picks up and maternal alloantibodies are cleared. Recent evidence from a randomized controlled trial showed that treatment with erythropoietin stimulating agents may be considered to reduce the need for RBC transfusions.[44]

Inherent to the disease's low prevalence and the challenges associated with performing long-term follow-up, research on long-term outcomes in HDFN has been limited. A handful of large cohort studies on the (neuro)development of children with HDFN managed in centers with relatively high expertise are available.[45-47] The few available cohort studies show favorable developmental outcomes among those affected.[45-47] An important aspect of research on long-term outcomes is the identification of risk factors for adverse outcome, previous research had shown that the prevention of severe fetal hydrops by timely referring at-risk pregnancies and early detection and treatment of those with fetal anemia may improve long-term outcomes.[46]

AIM AND OUTLINE OF THIS THESIS

With the considerably increased perinatal survival rates and decreased morbidity rates in affected patients over the past century, the overall stance of some experts in the international fetal-medicine community was that the management of HDFN had reached an '*as good as it gets*' state, especially in high-income countries. Specifically in the Netherlands, due to the national centralization of healthcare, many publications come from our country, and we have a good understanding of what is happening within our borders. However, without continuous monitoring of the performance of the state-of-the-art in an international perspective one might either drift from a high level of care or may miss opportunities to improve. We strongly believe that fostering a culture of continuous improvement for the benefit of our patients is something we should prioritize. This can be achieved by raising awareness through education, critically evaluating our current standards of care, enhancing multidisciplinary and international collaborations, addressing global health disparities, optimizing personalized care through improved diagnostic tools, refining the use of existing treatments, researching adjunctive or novel treatments, and monitoring long-term outcomes to help refine clinical management strategies. With these objectives in mind, the research in this thesis aims to enhance our understanding of the disease and its management and provide recommendations to ultimately improve the outcomes for those affected.

Overview (Part I)

In the first part we provide an overview of the current knowledge of HDFN and its history. Chapter 1 then describes the current standard-of-care of managing neonates with HDFN, recent scientific findings and evidence gaps.

Evaluating our current standards of care (Part II)

Part II then reports the findings of a literature review on the current antenatal and postnatal treatment landscape and outcomes in pregnancies, fetuses and neonates affected by RhD- and K-mediated HDFN in order to identify the burden of the disease, to identify evidence gaps in literature and to provide recommendations for future research (Chapters 2 and 3).

Enhancing multidisciplinary and international collaborations (DIONYSUS studies) (Part III)

Research in fetal-maternal medicine, or rare diseases, have largely relied on research performed by centers in high-income countries that each provide care to only a small number of pregnancies. International collaborations are therefore essential to perform

cohort studies of sufficient size to further enhance our understanding and to identify opportunities to improve care. Taking together the rarity of the disease and our findings from literature reviews, we hypothesized that large variations may exist between centers in the management of affected pregnancies, fetuses and neonates. *Part III* therefore focuses on our findings from an international, retrospective, observational cohort study (Worldwide Collaboration for Hemolytic Disease of the Fetus and Newborn (DIONYSUS)) that uncovered practice variations in the antenatal (Chapter 4) and postnatal (Chapter 5) management among centers. These chapters also report opportunities to improve care based on these unique findings, such as the potential beneficial clinical association of waiting for delivery until after 37 weeks and 0 days. Chapter 6 discusses our experience with the challenges of conducting observational research under the General Data Protection Regulation (GDPR).

Refining the use of exchange transfusions and predicting its need (WISE study) (Part IV)

Exchange transfusions have become increasingly rare owing to improved phototherapy and the implementation of guidelines. Considering that exchange transfusions should not be delayed to avert potentially severe or lethal consequences, clinicians preorder and prepare reconstituted whole blood exchange transfusion products before being able to assess the effect of phototherapy. However, studies on the use and waste of exchange transfusion products and the indications for which exchange transfusions are performed are lacking. To critically evaluate our current standard of care and to sustain a qualitatively high level of care, we aimed to procure knowledge on the indications for exchange transfusions, and knowledge on the actual use of blood products to prevent unnecessary waste of donor blood products (Chapters 7 and 8). This research was possible because of the centralized Dutch Blood Supply.

Also, to personalize care for pregnancies affected and to aid caregivers to anticipate the need for an exchange transfusion, we aimed to assess whether the need for an exchange transfusion in neonates with HDFN could be estimated antenatally by using the maximum maternal alloantibody titer and ADCC test results. Considering that the exchange transfusion frequency had decreased over the years and that the increased rarity could affect expertise on a national level, we hypothesized that fewer hospitals would be capable of performing exchange transfusions (Chapter 9).

Innovations to improve diagnostics and a potentially new treatment option (Part V)

Despite improvements in the identification of pregnancies at-risk of fetal anemia, current diagnostic tools (titer and ADCC) are struck by a relatively high false-positive rate. Also, the monocyte-ADCC is labor-intensive, costly, and requires radioactive material. Therefore, its implementation in non-centralized settings is largely unfeasible and the need for a simplified but strong predictive assay is high. Previous research has suggested a potential diagnostic role for IgG-Fc-glycosylation and binding of FcγRIIIa-V158 polymorphism in the identification of pregnancies at-risk of severe HDFN. We therefore evaluated the diagnostic potential of IgG-Fc-fucosylation, and we compared the potential clinical value of a novel flowcytometric assay for the prediction of severe HDFN to that of the standard maternal antibody titer and monocyte-ADCC-assay (Chapter 10).

In recent years, nipocalimab, a selective FcRn blocker, has been under development for the treatment of both autoimmune and alloimmune disorders, including early-onset severe HDFN in which fetal anemia develops before 24 weeks and 0 days gestation.[48] FcRn is thought to be the sole or the most important placental transporter for both maternal IgG to the fetal circulation and salvage receptor for circulating IgG.[48,49] Therefore, FcRn blockade may inhibit HDFN's pathophysiology by lowering maternal IgG and preventing the transport of pathogenic IgG to the fetus.[48,49] Results from 13 pregnancies that participated in a phase 2, international, open-label, single group trial showed that the use of nipocalimab resulted in a higher percentage of pregnancies with live birth at 32 week's gestation or later without IUT compared to the previous qualifying pregnancy.[49] Considering that nipocalimab reduces the transfer of both pathogenic and beneficial IgG to the fetus, neonatal immunity may be affected and further investigation is required to evaluate nipocalimab's impact on immune responses in infants (Chapter 11).[50]

Long-term outcomes to guide clinical management strategies (Part VI)

To advance and refine clinical strategies it is imperative to monitor long-term developmental outcomes and identify factors associated with adverse or favorable outcome. However, long-term follow-up in this pediatric population is challenging owing to a potential burden on the family and a lack of required personnel and material in an already strained healthcare system. Also, parents may not feel an incentive to attend follow-up because of the limited pathological extend of HDFN to three months postpartum, thereby also potentiating selection bias. Nevertheless, this essential dimension must be addressed in order to provide the best care to our patients.

We therefore assessed the long-term neurodevelopmental outcomes of infants who participated in a trial that evaluated the effect of erythropoiesis stimulating agents on the number of red blood cell transfusion episodes in newborns with HDFN who were treated with IUT[44] (Chapter 12).

To address the evidence gap on long-term neurodevelopmental outcome in HDFN we evaluated the neurodevelopmental outcomes of all infants with IUT at the LUMC in a retrospective, observational cohort study spanning a period of 35 years (Chapter 13). We additionally aimed to identify factors associated with cognitive score and neurodevelopmental impairment to support clinical policies such as the recommendation to wait for delivery until after 37 weeks and 0 days.

Discussion and summary (Part VII)

Finally, in *Part VII* of this thesis, we discuss the results of the chapters included in this thesis in light of the available literature highlighting its implications and new directions for research.

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