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Hemolytic disease of the fetus and newborn

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SUMMARY AND DISCUSSION

SUMMARY AND GENERAL DISCUSSION

EPILOGUE

NEDERLANDSE SAMENVATTING

SUMMARY AND GENERAL DISCUSSION

Hemolytic disease of the fetus and newborn (HDFN) is a serious condition that, if remained untreated, may result in fetal hydrops or even death. In the past decades, much has changed in the prevention, screening, monitoring and (intrauterine) treatment of HDFN. Outcome data of pregnancies complicated by even the severest forms of HDFN, at least in specialized tertiary care centers, are considered excellent, and generally regarded to have reached an 'as good as it gets' level. However, even in the best centers, fetal and neonatal death due to HDFN still occurs.

The aim of this thesis was to review and critically analyse current management for this disease and to assess factors that contributed to reaching this point, in order to provide specific tools to further improve outcome.

Chapter 1 provides an overview of the current state-of-the-art setting, technique and outcome of intrauterine blood transfusions (IUTs) for HDFN. Additionally, we summarize the available literature on two alternative (or additional) prenatal non-invasive treatment options: therapeutic plasma exchange and intravenous immunoglobulin treatment. The chapter concludes that IUT is nowadays considered a safe procedure in experienced hands, although complication rates of IUTs performed in early gestation remain relatively high. Maternal treatment with plasma exchange or intravenous immunoglobulins are thought to lower the pathogenic alloantibody levels in mother and child. From several case series these treatments have been postulated to delay the onset of fetal anemia and, hence, to postpone the necessity of early IUTs. To evaluate whether IVIg indeed may improve outcome in these cases, we performed an international cohort study, further described in Chapter 6 of this thesis.

Pathogenesis and prevention

HDFN is caused by maternal antibodies against fetal red cell antigens, usually provoked by fetomaternal hemorrhage during pregnancy or delivery. HDFN is most frequently caused by D (formerly known as RhD) alloantibodies, although alloantibodies with other Rh specificities (c, C, E, e) or non-Rh alloantibodies (K, Fy, Jk) may also induce fetal hemolysis. As a result of several preventive measures, of which anti-D immunoprophylaxis (RhIg) is the most important, both Rh and non-Rh alloimmunization in pregnancies is more and more becoming rare. Interestingly, the working mechanisms of RhIg remain partly unclear to date.

In 2016, 14.6% of the Dutch pregnant population (N=172,414) was D-negative and thus at risk for D antibodies. Only 156 pregnant women, out of this total pregnant population (D-negative and D-positive,) indeed had D antibodies. 94 were new immunizations; the prevalence was thus 0.09%, the incidence 0.05% (rates obtained by cohort study described in chapter 3, unpublished data). The prevalence of all types of RBC alloantibodies in pregnant women, including D, was 0.29-0.41%.[14] Importantly, apart from c-, E- and Kell-matching of red cell transfusions to women of reproductive age, no preventive measures are available to prevent these other immunizations. The pivotal observation in the 1940s that pregnancies of ABO incompatible couples were less often complicated by D immunization, led to a better understanding of the pathogenesis of D immunization and eventually to the development of RhIg as an important preventive measure.[4,131] However, as it is unknown whether this is also the case for non-D immunizations, we addressed in **Chapter 2** both the pathogenesis of these immunizations and the working mechanism of RhIg, by evaluating whether ABO incompatibility and RhIg also prevent the occurrence of non-D antibodies. We identified women with newly detected non-D antibodies, immunized during their first pregnancy and/or delivery. Of these 232 women (cases), 11.9% had a possible ABO incompatible pregnancy, significantly less than the expected 19.4% in the Dutch pregnant population (controls). We furthermore found that the subgroup of 99 women with only non-Rh antibodies had significantly less often received RhIg in their first pregnancies. These findings suggest that both ABO incompatibility and RhIg not only reduce the risk of D immunization, but also of non-D and non-Rh immunizations, respectively, implying that antibody-mediated immune suppression (AMIS) by RhIg is not antigen-specific. In our opinion, future attempts to manufacture the second generation of anti-D immunoprophylaxis, not dependent on the decreasing human donor pool, could focus on a fetal RBC-specific target. By doing so, a universal prophylaxis against the fetal red blood cell, to prevent all types of RBC alloimmunization, might be achievable.

An additional, perhaps more realistic, future perspective on immunoprohylaxis concerns combining the non-invasive prenatal testing (NIPT) for syndromal abnormalities with an extensive maternal and fetal antigen typing in the first trimester. Subsequently, a personalized tailor-made mix of engineered monoclonal antibodies can be administered based on the found incompatibilities. As we found that the AMIS response seems to be not antigen- specific, it might even be redundant to administer a prophylaxis for all incompatibilities separately.

Disease severity

Preventing red blood cell alloimmunization is of utmost importance, as this condition may have serious sequelae. A decade ago, Koelewijn et al. performed a nationwide Dutch cohort study amongst pregnant women with D immunization and found that in primiparae with first detected D antibodies, 19% of children needed an intrauterine transfusion (IUT), a neonatal exchange transfusion, or even died.[5] **In Chapter 3,** we investigated the expert opinion that disease severity increases in subsequent D alloimmunized pregnancies with D-positive children (thus at risk for HDFN), in a new nationwide Dutch cohort study. We found that this was indeed true, as most disease characteristics were more severe in second pregnancies at risk for HDFN, compared to the index (first immunized) pregnancy. For example, second pregnancies at risk showed higher titer and ADCC results, more fetuses treated with IUT, more births induced prematurely, lower neonatal hemoglobin and higher bilirubin levels and more children treated with phototherapy and neonatal red cell transfusions. It seemed that antibodies first detected at 27th week screening ('late') is in fact a sign of strong maternal respondership to a small fetomaternal hemorrhage during pregnancy, rather than a weak response to a previous birth. Although the group in which antibodies were already found at first trimester screening were most often immunized after giving birth to a D-positive child (relatively large hemorrhagic event) and had the entire extend of the pregnancy to develop substantial disease severity, the severity in the index pregnancy was equal to the late immunized group. Furthermore, disease severity did increase only in the group with late antibody formation, also indicating a more active immune response. It is not completely known why women are low or high-responders, although authors have postulated associations with certain HLA-DRB1 types.[154,230] Identification of 'high responders' early in pregnancy in the future might enable the administration of additional early RhIg, before antibody formation can occur. The antibody dependent cell-mediated cytotoxicity (ADCC) test result showed predictive for severe disease: if it did not exceed 10% in the index pregnancy, 94% of second D-positive children at risk did not need intrauterine transfusion(s). Based on the moment of antibody detection, antibody characteristics as reflected by ADCC test results and the disease severity in the index pregnancy, parents can now be properly counselled on the risk of severe disease in a subsequent pregnancy.

Already in the second pregnancy complicated by D immunization, almost a third of patients were in need for antenatal intervention by intrauterine transfusion (IUT). The Leiden University Medical Center has served as the national referral center for

fetal therapy since the introduction of intraperitoneal intrauterine transfusion in the Netherlands in the 1960s. In that era, no routine first trimester antibody screening was performed and patients referred for IUT often presented with (severe) fetal hydrops,[49] a condition associated with poor outcome on both the short and the long term.[31,32] The intraperitoneal IUT was gradually replaced by the ultrasound-guided intravascular IUT from 1987 onwards and routine early screening was implemented in 1998. **Chapter 4** describes how this and other measures have led to the near disappearance of severe alloimmune hydrops in the complete 30-year cohort of 645 fetuses treated with intravascular IUT in the Netherlands. Since routine screening before week 13 was introduced in 1998, fetuses at risk for anemia are identified and treated more timely. This is reflected by the finding that the proportion of fetuses first presenting with hydrops significantly declined from 40 to 16%. Strikingly, during the last six years of the study, only one fetus presented with severe hydrops. Thus, if hydrops occurs nowadays, it is usually mild. As mild hydrops is known not to be associated with impaired outcome,[31] survival of fetuses with and without hydrops is currently almost equal, rising up to or above 95%. This is a major gain in the outcome of fetuses suffering from HDFN in the Dutch setting. We postulate that this improvement is likely the result of a cascade of measures, including: the introduction of early screening for alloantibodies in all pregnancies, use of national guidelines and the availability of both national reference laboratories and the pooling of knowledge and expertise in a single referral center for fetal therapy.

Intrauterine transfusion

Another important step forward in the survival of IUT treated fetuses was to optimize transfusion techniques in order to lower complication rates. In **Chapter 5** we found, in approximately the same cohort as in Chapter 4, that the procedure-related fetal loss rate is currently as low as 1.8%. This rate decreased significantly over time and was relatively low compared to that of most other centers (this thesis, Table 2 of Chapter 1). An important factor probably influencing this decrease is the large number of IUTs performed annually in our center, as a result of the Dutch approach to centralize fetal therapy. Thus all IUTs, a critical and skill-demanding procedure, that are needed in the Dutch pregnant population of approximately 180,000 pregnant women annually, are performed in our national referral center. These large volumes both enable the identification of technical risk factors, such as transfusing into a free loop of cord or refraining from applying fetal paralysis, to optimize the methods used, and the existence of a highly experienced team of operators, sonographers and specialized nurses, to increase safety and efficacy of these complex procedures.[95] Therefore, we advocate

centralization of fetal therapy in larger volume centers to profit from the 24/7 availability of an optimally trained team to consult and refer to and to benefit from up to date knowledge and care.

The safest transfusion techniques, as described in Chapter 5 and other studies, are transfusing into the placental cord insertion or the intrahepatic part of the umbilical vein.[89] In **Chapter 4** an additional advantage of the intrahepatic technique was presented: the possibility to leave an intraperitoneal blood deposit, in order to potentially prolong the inter-procedure interval. If performed at the last intrauterine transfusion, such a deposit was associated with a higher neonatal hemoglobin level.

Our finding that current monitoring and treatment of HDFN affected fetuses has reached a 'as good as it gets' state, does not apply to fetuses in need for early transfusion. It is known, and confirmed in Chapter 5, that transfusions performed before 20-22 weeks' gestation carry a substantially higher risk for adverse outcome.[96-99] Probably due to the technical difficulties of transfusion at this early gestational period, fetal death rate in this group unfortunately did not decrease significantly over time in our cohort. Therefore, evidence based alternative treatment options to postpone or entirely preclude the need for IUT are urgently required.

Alternative treatment options

As summarized in Chapter 1, therapeutic plasma exchange (TPE) and/or intravenous immunoglobulins (IVIg) are frequently proposed as alternatives for early intrauterine transfusion. The current experience mostly concerns case series with promising yet contradicting results, prospective trials performed on this topic are lacking. Probably, this results from the fact that such severe HDFN is very rare, troubling the sample size of single center studies. We therefore performed an international multicenter study among women with a history of severe HDFN. The results of this PETIT study (Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment) are described in **Chapter 6**.

Pregnancies of mothers with a previous first IUT before 24 weeks or a previous HDFN-related fetal or neonatal death that were treated with IVIg in the next pregnancy, were compared to non-IVIg treated mothers with a similar history. As clinical reasons undoubtedly have influenced the choice whether or not to treat these women with IVIg, we aimed to adjust for this 'confounding by indication' by performing propensity analysis.

We found that IVIg treatment was associated with less fetal hydrops and less neonatal exchange transfusions. Furthermore, treatment with IVIg postponed the first IUT with 15 days, compared to that in the previous pregnancy, and with a non-significant adjusted 4 days compared to the non-IVIg group. If IVIg was started early, before 13 weeks' gestation, the effects were more profound. In general, the estimates of all outcomes pointed in the same direction: a possible clinically relevant effect of IVIg on the course and severity of disease in this severely affected group of patients. A prospective, multicenter and preferable randomized trial (RCT) is needed to truly settle the dispute whether IVIg postpones the onset of alloimmune anemia and thus the need for early transfusions. Based on our results however, it is unlikely that IVIg will completely preclude the need for treatment with IUT and therefore other immunomodulatory agents should additionally be evaluated.

The reasons that we advocate performing a randomized trial on the effect of IVIg, although our results already indicate a beneficial effect, are described in **Chapter 7** of this thesis. This chapter contains a Cochrane systematic review on the use of neonatal IVIg to prevent the need for postnatal exchange transfusion. Although IVIg appeared favourable in case series and even in small randomized trials, such a beneficial effect of IVIg administration to the newborn was not found in two high quality randomized and double blinded RCT's. No differences were seen in the need for exchange transfusions or in the number of exchange transfusions per infant in these two studies at low risk of bias. Furthermore, IVIg is expensive and concerns have been raised on a possible correlation between neonatal IVIg treatment and necrotizing enterocolitis. Lastly, the use of high quality intensive phototherapy gradually precludes the need for exchange transfusions in developing countries. The review concludes that there is insufficient evidence of the efficacy of neonatal IVIg for HDFN and therefore the neonatology department of the Leiden University Medical Center advocates against the routine use for this indication.