Improving care for red blood cell alloimmunized pregnant women

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Chapter 10

Summary

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Pathogenesis and prevention

Hemolytic disease of the fetus and newborn (HDFN) is caused by red blood cell (RBC) alloantibodies, developed by the mother and transferred to the fetus. Most severe cases are caused by RhD, Rhc and K antibodies. Without treatment, HDFN may result in progressive fetal anemia, fetal hydrops, asphyxia and perinatal death. The introduction of this thesis (**Chapter 1**) provides information about the development during the years of the Dutch national program to prevent and timely detect RBC alloimmunization in pregnant women. This program resulted in a decrease in the incidence of RBC alloimmunization and, more importantly, in reduction of perinatal morbidity and mortality. The so-called Prevention and Screening of Infectious Diseases and Erythrocyte Immunization (PSIE) program, currently encompasses respectively prevention of anti-D formation by provision of RhIg prophylaxis (antenatal and postnatal doses); screening for RBC alloantibodies at the booking visit and in RhD-an Rhc-negative women at 27th week of pregnancy. During the years, also the Dutch Transfusion Guideline developed into a policy with matching blood transfusions for Rhc, D, E and K in women below 45 years of age. The timely detection of HDFN has ensured that alloimmune fetal hydrops is rare nowadays. For RhD immunized pregnancies, which remains the most prevalent cause of severe HDFN, selection of high-risk cases and reassurance of low risk by laboratory testing is specific and valid. This was much less well defined for K-immunized pregnancies or if other type of Rh type immunization is present. as described in **Chapter 1**.

As introduced in **Chapter 1**, to identify elements in the RBC alloantibody screening and prevention program that could be improved, the Can Meds framework can be used as a starting point. It can also be used to evaluate the provided care to RBC alloimmunized pregnant women. Therefore, in this thesis, the tools of the Can Meds framework were used to formulate study questions and steps to improve the care.

Incidence and prevalence of RBC alloimmunization

In **Chapter 2** and **3** we evaluated the current incidence of RhD and Rhc immunization in the Netherlands. We evaluated this in two national cohorts. In addition, we also looked at risk factors for RhD immunization and lately detected Rhc immunizations. The prevalence of newly detected RhD immunizations in 2016 was 0.31% (79/25,170) of all RhD-negative pregnant women in the Netherlands. The prevalence of all RhD immunizations (including pregnancies from women who were likely immunized before immigration to the Netherlands) in 2016 was 0.09% of all pregnant women

(158/171,727) and 0.63% of RhD-negative pregnant women in the Netherlands (rates described in **Chapter 2**). In our nationwide cohort (2011-2013) we found 99 Rhc-negative (0.16%) women with newly detected RBC antibodies with the second RBC alloantibody screening at 27 weeks of gestation **(Chapter 3)**. We observed that a previous pregnancy (delivery) was an important risk factor for development of anti-c during the subsequent pregnancy (RR parity (P1: OR, 11.8; 95% CI, 3.00–46.5; P > 1: OR, 7.77; 95% CI, 1.70–35.4). We recommend considering restricting 'week 27 screening' to only those Rhc-negative women with a foregoing pregnancy (55%). Such a policy would improve the number needed to screen (NNS) from 31048 (if screened all) to 17076 (if only ≥P1 would be screened).

Risk factors for RBC immunization

In **Chapter 2** we identified risk factors for fetal maternal hemorrhage (FMH) resulting in RhD immunization despite antenatal and postnatal prophylaxis. In a cohort of 194 women in their first immunized pregnancy, there were 113 women with a foregoing pregnancy above 16 weeks gestation assumed as "exposed" to the RhD antigen. In this group, risk factors for RBC alloimmunization present in a foregoing pregnancy were cesarean section (CS) (OR 1.7, 95% CI 1.1-2.6), perinatal death (OR 3.5, 95% CI 1.1-10.9), gestational age over 42 weeks (OR 6.1, 95% CI 2.2-16.6), postnatal bleeding (>1000mL) (OR 2.0 95% CI 1.1-3.6) or surgical removal of the placenta (SRP) (OR 4.3, 95% CI 2.0-9.3). In the group of nulliparous women and women without an RhD positive child in the previous pregnancy, assumed as "non-exposed" or "possibly" exposed to the RhD antigen, there were no risk factors related to possible events leading to FMH during pregnancy found. Remarkably, we observed a considerable higher miscarriage rate (35%) in this group compared with the average population (12,5%).

Risk factors for late alloimmunization in Rhc-negative women are described in **Chapter 3.** In addition to the data presented in **Chapter 2** for RhD-negative women we found in Rhc-negative women that invasive diagnostic in early pregnancy was a risk factor for Rhc immunization in pregnancy. No other risk factors related to the current pregnancy were identified that might have led to late Rhc immunization detected in week 27 of pregnancy. Independent risk factors for late alloimmunization were blood transfusion in history (OR 10.4; 95% CI, 1.14–94.9), parity (P1: OR, 11.8; 95% CI, 3.00–46.5; P > 1: OR, 7.77; 95% CI, 1.70–35.4) and chorionic villus sampling/ amniocentesis (OR, 9.20; 95% CI, 1.16–72.9) in the current pregnancy.

Donor recruitment

With the effectiveness of the prevention program, the number of RhD-immunized women and thus potential anti-D donors has decreased. In **Chapter 4** it is described that recruiting anti-D donors would benefit from a targeted approach. A lack of knowledge about the possibility to become an anti-D donor was found to be the main barrier to become one. When RhD-immunized women know about this possibility almost 70% of those who were not yet an anti-D donor indicated that they might have become donors if they had been informed. Motivators to become anti-D donors were “want to do something in return” (31%) and “want to prevent others having a sick child or losing a child” (34%). The negative factors we identified were time investment and travel time investment, but 50% of the interviewed anti-D donors mentioned no negative factors of being an anti-D donor.

Timely detection and monitoring

To timely identify pregnancies at risk for a severe course of HDFN, defined as a need of fetal therapy, induced preterm delivery or intensive neonatal treatment, repeated laboratory testing during pregnancy is advised. In this pre-selected group of alloimmunized women, fetal anemia can be diagnosed with a high sensitivity and specificity by non-invasive ultrasonography, using Doppler middle cerebral artery blood (MCA) flow velocity measurements. The tests used for repeated laboratory testing during pregnancy are determination of the RBC antibody titer and antibody activity with the antibody dependent cellular cytotoxicity assay (ADCC). These tests are well validated in RhD-immunized pregnancies, but less well if RBC alloantibodies other than anti-D are present. In **Chapter 5** we evaluated the diagnostic value of the ADCC and titer in case of K-alloimmunized pregnancies with a K-positive fetus. The first measured titer with a value above 4 has the best performance in identifying cases with the need for IUT or postnatal transfusion therapy: sensitivity 100% (95% confidence interval, 91-100); specificity 27% (95% confidence interval, 15-43), and positive predictive value of 60% (49-71%). The ADCC test was not informative to select high-risk pregnancies. Linear regression showed no significant change during pregnancy, when antibody titer and ADCC test results were compared with every 2 foregoing measurements ($P < 0.0001$). Furthermore, we observed in a cohort of 93 pregnancies with a K-positive fetus that >50% of K-positive fetuses need either intrauterine transfusion or postnatal transfusion therapy.

In **Chapter 6** we evaluated test characteristics of RBC alloantibodies with another specificity than anti-D or anti-K. We used a cohort collected recently in 2015-2016 and compared the results with a cohort collected in 2003-2004 of which also HDFN disease severity was collected. The optimal cut-off value for the maximum titer in

pregnancies with an antigen-positive fetus was ≥ 16 with a sensitivity of 100% and a specificity of 67% to predict severe HDFN (need for antenatal or postnatal transfusion). On average in 18% of the pregnancies the cut-off value for the titer was reached; but a higher percentage of 36% was observed if anti-c was present. We calculated the positive predictive value (PPV) of the titer to be only 17%, and if in combination with an ADCC of ≥60% the PPV is 60% (83% if anti-c is present, 25% for other type of antibodies. Based on these results we present in the **General Discussion** a proposal to use extensive laboratory monitoring for high-risk case selection in RhD, Rhc and K alloimmunized pregnancies, and to be more restricted with repeat testing if other type of RBC alloantibodies is present.

The prevention program from health care provider and patient perspective

The low prevalence of RBC alloimmunization and especially the rare occurrence of severe HDFN may result in insufficient knowledge and subsequent inadequate transfer of information to pregnant women, diagnosed with RBC alloantibodies. In **Chapter 7** we measured knowledge, attitude and practices (KAP) regarding maternal RBC alloimmunization among Dutch obstetric care providers. We found that only 7% of 329 participants had sufficient knowledge of all aspects of maternal RBC alloimmunization as judged needed to provide sufficient support and counselling during pregnancy. The knowledge gaps we found concerned respectively aspects of alloimmunization with non-RhD alloantibodies, the interpretation of ADCC and antibody titer results and indications for administering extra doses of RhIg.

Next, we set out a study to investigate how women with a pregnancy complicated by RBC alloantibodies experience the provision of information, the transfer to a specialized hospital and how this all influenced their experience of the pregnancy. In **chapter 8** we describe that woman noticed that the knowledge of the healthcare provider was insufficient to provide satisfactory information about RBC alloimmunization and risks for the fetus. Poorly provided or incomplete information after detection of RBC alloantibodies, or during follow-up, influenced their confidence in a positive pregnancy outcome and caused feelings of anxiety. The study also showed that if the caregiver is aware of the limits of the own knowledge and skills and consults an expert with questions or uncertainties, this shortcoming can be overcome.

In the **General Discussion** our findings in the Dutch context. To put the prevention program in a broader context, we have used the Can Meds framework. Viewed from the perspective of the different roles of a healthcare professional, it can be concluded that the roles of collaborator, leader and medical expert are very much

used and necessary in the care to women with RBC alloimmunization. The rare occurrence of RBC alloimmunization and HDFN makes it difficult to provide sufficient and correct information to RBC alloimmunized pregnant women. Although experts can be consulted, there is also room for improvement to provide a clear guideline and easy access to correct information. Knowledge of the disease can personalize the moments of laboratory and clinical testing. Overall, it was observed that there is still a lot that can be achieved when investing in training of health care providers on theoretical background of the red blood cell alloimmunization prevention program and in the counselling of pregnant women with RBC alloimmunization and at risk of HDFN. The Can Meds roles of communicator, professional and lifelong learning (scholar) represent the challenges of obstetric care providers and investment in those roles would further add to the already high level of care to the small group of women with a pregnancy at risk of HDFN. Finally, the obstetric care provider can certainly also take the role of health advocate, since there are still opportunities to make RhIg more widely available to reduce morbidity and mortality of HDFN on a global level.