

ABSTRACT

The general purpose of this thesis was to investigate if fetal and neonatal complications due to RhD immunization in the mother could be prevented by 1) reducing procedure-related complications in intrauterine blood transfusions and by 2) reducing the incidence of RhD immunization by providing routine antenatal anti-D prophylaxis during pregnancy selectively to non-immunized RhD negative women with RhD positive fetuses.

Paper I was a retrospective study including 284 intrauterine transfusions in 84 women 1990-2010. Perinatal survival was 91.8 %. Complications occurred in 4.9 % of procedures of which 1.4 % were fatal. Procedure-related complications were significantly more common when transfusions were performed in a free loop of the umbilical cord compared to the intrahepatic part of the umbilical vein (OR 5.4, 95% CI: 1.2 to 23.7, P=0.025). There was no significant difference between the intrahepatic route and the placental cord insertion (P=0.83).

Paper II was a pharmacokinetic study on 16 women measuring plasma concentrations of anti-D IgG at predefined time points after administration in gestational weeks 28-30. The half-life was in median 23 days (12.5 - 30.3). At ten weeks after injection, plasma concentrations ranging from 1-4 ng/mL were found in all samples available for analysis. We estimated that 75 % of women would have had detectable anti-D IgG concentrations ≥ 1 ng/mL at the time of delivery.

In paper III we performed a large prospective cohort study on the diagnostic accuracy of a single-exon noninvasive method to determine fetal *RHD* genotype in the first trimester of pregnancy. Plasma samples from 4118 pregnancies were included in the analysis. Median gestational age for blood sampling was 10 weeks. From eight gestational weeks, sensitivity was 98.9 % (95% CI 98.3 - 99.3) and specificity 98.9 % (95% CI 98.1 - 99.4). From 10 weeks of gestation sensitivity was 99.3 % and from 22 weeks 100 %.

Paper IV was a retrospective study on all (290) RhD immunized pregnant women in Stockholm 1990-2008. Fifty-one % (147/290) of the women were sensitized with their first-born child and 33 % (96/290) with their second born child. At least half of the women were immunized in the third trimester, which could possibly have been prevented with antenatal prophylaxis. Fifty-six % (144/259) of the neonates in subsequent pregnancies required treatment for hemolytic disease, independently of in which order or pregnancy the women were immunized.

In paper V we performed a prospective cohort study offering anti-D prophylaxis in gestational week 28-30 selectively to all RhD negative pregnant women in Stockholm with an *RHD* positive fetus. Selective prophylaxis was provided in 4590 pregnancies resulting in an incidence of RhD immunization in the study cohort of 0.21 percent (95% CI 0.12 - 0.31) (20/9380). The reference cohort consisted of all RhD pregnant women giving birth in the same region 2004-2008 and the incidence in this group was 0.46 percent (95% CI 0.37 - 0.56) (86/18,546). The risk ratio (RR) for sensitization was 0.46 (95% CI 0.28 - 0.75) with the new program.

This thesis shows that without routine antenatal anti-D prophylaxis, the majority of women become RhD immunized during pregnancy with their first or second child. The risk of hemolytic disease of the fetus and newborn is the same regardless of in which order of pregnancy a woman become immunized and occurs in more than half of subsequent pregnancies. Non-invasive fetal *RHD* genotyping in the first trimester of pregnancy can be performed with high accuracy and enables administration of routine antenatal anti-D prophylaxis (RAADP) selectively to RhD negative women with *RHD* positive fetuses. This reduces the risk of RhD immunization to 0.21 percent. RAADP usually lasts for ten weeks after injection but thereafter concentrations are variable and not all women will have detectable anti-D levels at term and post-term, which might be a cause of residual immunizations. Perinatal survival in pregnancies requiring intrauterine blood transfusion is high, but the risk of procedure-related complications can be further reduced by applying a safer technique and with timely referrals to a specialized center before severe anemia develops.