Rhesus Haemolytic Disease of the Newborn

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STUDENT REPORT

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Rhesus hæmolytisk sygdom hos nyfødte

Dansk resume

Rhesus immunisering er en af hovedårsagerne til hæmolytisk sygdom hos nyfødte. Behandlingsmetoderne af Rhesus hæmolytisk sygdom er intrauterin transfusion, udskiftningstransfusion, transfusion med røde blodceller, lysterapi samt intravenøs immunglobulin. I Danmark gives Rhesus anti-D profylakse til ikke-immuniserede Rhesus D negative kvinder i graviditetsuge 28, efter abort og efter fødsel for at forebygge hæmolytisk sygdom, hvis de bærer et Rhesus positivt foster. Til trods for dette fødes flere børn med Rhesus hæmolytisk sygdom.

Formålet med dette retrospektive kohorte studie var at bestemme incidensen af Rhesus hæmolytisk sygdom, antallet af nyfødte som blev behandlet med intrauterin transfusion, udskiftningstransfusion, transfusion med røde blodceller, lysterapi og intravenøs immunglobulin i Region Nordjylland gennem perioden 2005 til 2014. Herudover at undersøge om incidensen, maksimum plasma bilirubin koncentrationen samt varigheden af behandlingen med lysterapi faldt gennem perioden.

ICD-10 diagnosesystemet blev brugt til at identificere de nyfødte diagnosticeret med isohæmolytisk sygdom i Region Nordjylland. Journaler og laboratorieskemaer fra Børneafdelingen, Gynækologisk og Obstetrisk Afdeling samt Blodbanken, Aalborg Universitetshospital, Aalborg, blev brugt til indhentning af data (n = 100). 67 nyfødte blev inkluderet i studiet, mens 33 blev ekskluderet pga. negativ direkte antiglobulin test, autoimmunisering af barnets moder eller manglende information på den direkte antiglobulin test. De inkluderede nyfødte blev inddelt i følgende grupper: Rhesus D gruppe (n = 41), Andre-Rhesus gruppe (n = 15) og Non-Rhesus gruppe (n = 11). Ingen af de nyfødte havde sepsis eller var tvillinger.

Følgende obstetriske og neonatale data blev registreret: antal nyfødte behandlet med intrauterin transfusion, udskiftningstransfusion, transfusion med røde blodceller og/eller intravenøs immun-

globulin, gestationel alder ved fødsel, fødselsvægt, Apgar ved 1 minut, fødselsår, direkte anti-globulin test ved fødsel, blod-hæmoglobin og plasma bilirubin ved fødsel, maksimum plasma bilirubin under behandling samt enkel/dobbel lysterapi.

Statistiske analyser blev lavet ved brug af den uafhængige t-test til kontinuerlige variable samt Fishers eksakte test til kategoriske variable. Associationen mellem fødselsåret og incidensen, gennemsnits maksimum plasma bilirubin samt gennemsnitsvarigheden af lysterapi blev beskrevet med både lineær regression og spline-kurve med 3 punkter. De statistiske analyser blev lavet vha. computerprogrammerne STATA og SPSS. Statistisk signifikans blev sat til 5 %.

Den totale incidens af isohæmolytisk sygdom var 1,22 ‰, hvoraf Rhesus D immunisering udgjorde 0,75 ‰. Incidensen af Rhesus D immunisering havde en faldende tendens gennem perioden. Der var flest immuniseringer med Rhesus D, hernæst Rhesus c og Rhesus E. Non-Rhesus gruppen i dette studie bestod af 8 forskellige antistofsammensætninger, som hver især har forskellige sværhedsgrader, hvorfor denne gruppe ikke blev undersøgt yderligere. Antallet af immuniseringer med et enkelt antistof og multiple antistoffer var næsten lige stor.

Nyfødte med Rhesus D immunisering havde et alvorligere sygdomsforløb end nyfødte med anden Rhesus immunisering, hvor Rhesus D blandt andet viste sig med en lavere gestationel alder og fødselsvægt, flere preterm fødte samt lavere navlesnors blod hæmoglobin og direkte antiglobulin test. Maksimum plasma bilirubin koncentrationen steg signifikant, mens gennemsnitsvarigheden af lysterapi var konstant gennem hele perioden, hvilket muligvis kan skyldes en mere afslappet holdning til moderate plasma bilirubin niveauer, samt at dobbel-lysterapi muligvis bliver brugt mindre i de senere år i forhold til de tidligere. Konklusionen var at Rhesus D immunisering havde en faldende tendens gennem perioden, maksimum plasma bilirubin koncentrationen steg signifikant, mens gennemsnitsvarigheden af lysterapi var konstant gennem perioden.

Rhesus Haemolytic Disease of the Newborn

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Keywords: Rhesus haemolytic disease of the newborn, isoimmunization, intrauterine transfusion, exchange transfusion, top-up red blood cell transfusion, intravenous immunoglobulin, phototherapy.

Abbreviations:

IUT – intrauterine transfusion

ET – exchange transfusion

PT – phototherapy

IVIg – intravenous immunoglobulin

DAT – direct antiglobulin test

LED – light emitting diodes

ABSTRACT

Background: Rhesus immunization is one of the main causes of isohaemolytic disease in newborns. In Denmark Rhesus anti-D-prophylaxis is administered to non-immunized Rhesus D negative women during pregnancy, after abortion and after childbirth, to prevent the disease. Despite this, several neonates are born with Rhesus haemolytic disease.

Aim: The aim of this study was to determine the incidence of Rhesus haemolytic disease, the number of infants treated with intrauterine transfusion, exchange transfusion, top-up red blood cell transfusion, phototherapy and intravenous immunoglobulin in North Denmark Region during the

period 2005-2014. Furthermore, to investigate whether the maximum plasma bilirubin concentration and the duration of the phototherapy decreased during the study period.

Methods: In this retrospective cohort study, the ICD-10 revision codes system was used to identify the infants diagnosed with isohaemolytic disease in The North Denmark Region during the period 2005 – 2014. Data was extracted from journals from the Department of Paediatrics, the Department of Gynaecology and Obstetrics and the Blood Bank in Aalborg University Hospital (n = 100). 67 infants were included in the study and 33 were excluded because of a negative direct antiglobulin test, autoimmunization of the mother or missing information on direct antiglobulin test.

Results: The total incidence of isohaemolytic disease was 1.22 ‰ of which Rhesus D immunization represented 0.75 ‰. The incidence of Rhesus D immunization tended to be decreasing through the period. The number of immunizations with single and multiple antibodies was nearly equal. Infants with Rhesus D immunization were more severely affected than infants with other Rhesus immunization. Maximum plasma bilirubin concentration significantly increased while the average duration of the phototherapy was constant throughout the period, probably due to less aggressive treatment.

Conclusion: The incidence of Rhesus D immunization tended to be decreasing during the period. The mean maximum plasma bilirubin concentration significantly increased while the average duration of the phototherapy was constant throughout the period.

INTRODUCTION

During pregnancy the mother can be immunized against antigens on blood cells of the foetus. If the antibodies are of IgG-class, they can pass placenta in the present pregnancy or on later pregnancies and induce destruction of the foetus' blood cells (1–3). Immunization is believed to cause no adverse health effects to the mother. The firstborn is usually not harmed as the pregnancy is

generally completed by the time that immunization occurs (4). The infant may suffer fatal injury or lifelong sequalae (2,5).

Immunization is a non-reversible state and cannot be discovered by the pregnant woman herself (3). A woman is immunized against antigens which she does not have herself but the foetus has got from the father. The immunization may result in haemolysis of the foetal red blood cells. As a consequence the foetus develops anaemia which may lead to hydrops foetalis (3), which, if untreated, may have a fatal outcome (1). Haemolysis leads to excess production of bilirubin in the foetus. In uterus this is not a problem because the unconjugated bilirubin can pass the placenta. After birth, the neonatal liver cannot cope the large amount of bilirubin, which results in jaundice of the infant. At low plasma levels, unconjugated bilirubin is not harmful, whilst high plasma levels may result in deposition of bilirubin in the basal ganglia and cerebral nuclei in the neonatal brain, which can cause permanent brain damage or in severe cases have fatal consequences (2).

AB0-isoimmunization is the most common type of immunization, but it will not be discussed further in this study. Rhesus blood group system is also a common and the most important cause of maternal isoimmunization. It comprises the D, c, C, e, E antigens (2). The most common immunization is against antigen Rhesus D (2,3). The incidence of haemolytic disease is correlated to the number of persons with Rhesus negative blood type in the population. The prevalence of Rhesus D negative blood types varies with ethnicity. The Caucasians have the highest prevalence. When immunization has occurred, the pregnancy is at risk and the following examinations are needed: maternal antibody titre, partner genotyping and foetal blood group. Although some correlation exist between the antibody titre and the severity of disease, the level of antibody titre does not predict the severity of disease (2).

All pregnant women are examined for irregular antibodies during week 6-8 and week 25 of their pregnancy. Those with clinically significant antibodies are followed in order to identify the foetuses at risk of developing anaemia. This involves examination of the foetal Rhesus status using a blood sample from the mother and repeated ultrasound scans including Doppler measurements of the peak velocity of the middle cerebral artery, which tells when to give intrauterine transfusion (IUT) in case of foetal anaemia (2).

The Rhesus anti-D prophylaxis is given to non-immunized mothers with Rhesus D negative blood type (6). The prophylaxis is given by an intramuscular injection of 1250-1500 IU IgG-anti-D within 72 hours after birth of a Rhesus positive infant and since year 2009 it has also been given antenatal about pregnancy week 28-29. Furthermore, prophylaxis is given after amniocentesis, chorionic villous biopsy, antepartum haemorrhage, intrauterine foetal death, abortion and after surgery of an ectopic pregnancy (2,3,7). Women can be immunized despite adequate Rhesus anti-D prophylaxis in cases where the bleeding is larger than the Rhesus anti-D can block (3). There is no prophylaxis against other blood type immunizations.

In the postnatal period the treatment of immunization includes exchange transfusion (ET), top-up red blood cell transfusion, phototherapy (PT) and IV immunoglobulin (IVIg). ET removes both bilirubin, red blood cell antibodies and the red blood cells while top-up red blood cell transfusion corrects late anaemia (8). PT lowers bilirubin through changes of the bilirubin molecules and these can be excreted via bile and urine.

AIM

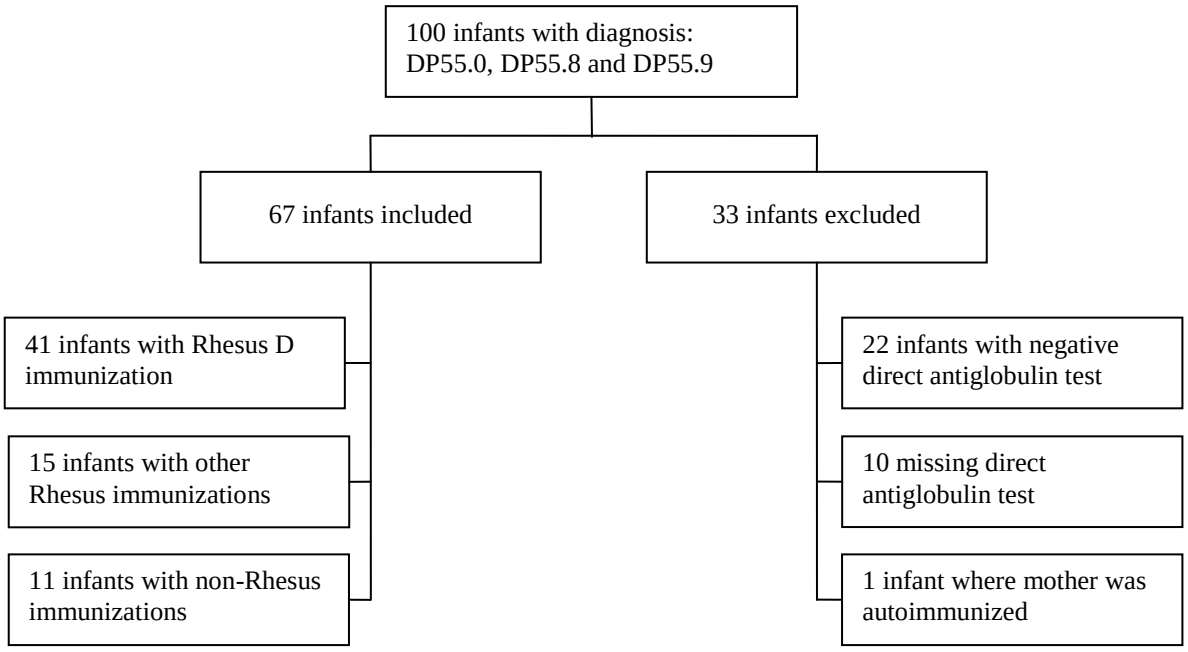
The aim of this study is to determine the incidence of isohaemolytic disease especially the Rhesus D immunization, the frequency of treatment with IUT, ET, top-up red blood cell transfusion, IVIg and

PT in infants born in North Denmark Region during the period 2005-2014. Furthermore, to investigate whether the incidence of Rhesus D immunization, the maximum plasma bilirubin (p-bilirubin) concentration and the duration of the PT decreased during the study period.

MATERIALS AND METHODS

In this retrospective cohort study the International Classification of Diseases 10th revision codes, DP55.0 Rhesus immunization of the foetus and newborn, DP55.8 Other types of haemolytic disease of foetus and newborn and DP55.9 Haemolytic disease of foetus and newborn without specification, have been used to identify infants diagnosed with isoimmune haemolytic disease in The North Denmark Region during the period of 01.01.2005 to 31.12.2014. The study was approved by the Committee for Biomedical Research Ethics.

Figure 1: Flowchart, inclusion and exclusion criteria



Data was extracted from journals and laboratory tests from the Department of Paediatrics, the Department of Gynaecology and Obstetrics and the Blood Bank in Aalborg University Hospital (n = 100). As shown in the flow chart (**Figure 1**) sixty-seven infants were included in this study and

the remaining were excluded because of a negative direct antiglobulin test (DAT), auto-immunization of the mother or missing information on DAT (n = 33). None of the infants suffered from sepsis and none were twins.

Following obstetric and neonatal data were recorded: number of infants treated with IUT, ET, top-up red blood cell transfusion and/or IVIg, gestational age at birth, body weight at birth, Apgar at 1 minute, birth year, foetal DAT at birth, blood-haemoglobin (Hb) and p-bilirubin levels at birth, maximum p-bilirubin levels during treatment period, duration of PT and single/double PT. Not all data were available for each case.

Asphyxia was defined as following: no asphyxia: Apgar/1 minute = 8-10, mild asphyxia: Apgar/1 minute = 5-7, moderate asphyxia: Apgar/1 minute = 3-4, severe asphyxia: Apgar/1 minute = 0-2.

IUT was performed at Department of Gynaecology and Obstetrics, Rigshospitalet, Copenhagen. ET replaced the infant's blood volume (85 ml/kg) two times through the umbilical vein.

The patient administration system was used to find the total number of births each year in North Denmark Region.

PT was administered continuously, except during feeding, nursing care, and blood sampling. During PT treatment with single light, the light source was placed above the infant, while it was placed both above and below during double light PT. Until primo 2008, blue fluorescent lamps (Philips 20WTL/BB) were used to PT. After 2008, blue light emitting diodes (LEDs) (neoBlue LED phototherapy device), were used for single light treatment. It was supplemented by a Biliblanket (Bilisoft phototherapy system) for double light PT. We were not able to compare the intensity of fluorescent lamps and LEDs but usually LED is considered more intensive than fluorescent lamps. This is due to the fact that the distance between the device and infant can be reduced as LEDs produce less heat than fluorescent lamps.

The indications for ET, IVIg and PT followed the guidelines from The Danish Paediatric Society.

Statistical analysis was performed using independent two tailed t-test for continuous variables, as appropriate. Fisher's exacts test was used for categorical variables. The association between the birth year and incidence, mean maximum p-bilirubin level and duration of PT was described both by linear regression and smooth regression by cubic splice with 3 knots. A test for linearity was performed by testing if the cubic spline relationship could be reduced to a simple linear relationship. Statistical analysis was executed with computer software (STATA and SPSS). Statistic significance level was ≤ 5 %.

Literature search was conducted respectively in Pub Med and EMBASE. Following Mesh terms were used "Rh isoimmunization", "Rho (D) immune globulin" with the free words "Rh/Rhesus isoimmunization/isoimmunisation", "Rh/Rhesus sensitization/sensitisation", "Rh/Rhesus alloimmunization/alloimmunisation", "immune globulin", "anti-D immunoglobulin", "Rh D antibody" all combined with following Mesh terms "neonatal hyperbilirubinemia", "infant, newborn" and the free words "neonate, neonatal", "infant, newborn", "erythroblastosis, neonatal", and "infancy hyperbilirubinemia". Limits were set for time (last 10 years), species (human) and language (English, Danish, Swedish and Norwegian) resulting in 1137 articles, some of them duplicates. Titles and abstracts were screened and 19 articles were chosen for this study. Latest search was performed 16.12.2015.

RESULTS

Table 1 shows the demographic and clinical data for the population in this study. There were 41 infants with Rhesus D immunization, 15 with other Rhesus immunization and 11 with non-Rhesus

immunization. The total incidence of isohaemolytic disease was 1.22 ‰ of which Rhesus D immunization represented 0.75 ‰. The gestational age, number of preterm births, the birth weight and the umbilical cord Hb were significantly lower and DAT was significantly higher for Rhesus D immunized infants than for other Rhesus immunized infants.

Table 1: Demographic and clinical data for neonates with isoimmune haemolytic anaemia

		Rhesus D group	**Other-Rhesus group**	**Non-Rhesus group**	**p-values between Rhesus D and Other-Rhesus group**
Number of newborns		41	15	11	
Incidence, ‰		0.75	0.27	0.20	
Gestational age, days (SD)		255 (19)	270 (5)	250 (24)	0.005
Preterm (< 259 days), n		18	0	5	0.001
Birth weight, g (SD)		2858 (744)	3321 (393)	2692 (846)	0.003
Sex, n	Males	16	7	4	0.76
	Females	25	8	7	
Ethnicity, n	Caucasian	32	13	10	0.71
	Non-Caucasian	9	2	1	
Umbilical cord	B-Haemoglobin, mmol/L (SD)	8.9 (2.3)	10.1 (1.8)	8.8 (2.0)	0.05
	P-Bilirubin, µmol/L (SD)	77 (41)	54 (29)	55 (16)	0.49
Degree of asphyxia, n					
No asphyxia		30	13	9	0.42
Mild asphyxia		5	1	1	0.66
Moderate asphyxia		2	0	0	
Severe asphyxia		0	0	1	
Direct antiglobulin test					
Severely positive		24	8	2	0.04
Moderate positive		10	1	4	
Mild positive		1	3	5	
Unspecified positive*		4	3	0	
Negative**		2	0	0	

* The test was performed without any specification of severity.
** DAT can be negative if the infant has had IUT.

Table 2 shows all the represented antibodies in the population, of which Non-Rhesus group consists of 5 different kinds of antibodies while **Table 3** shows whether the immunizations are with a single antibody or with multiple antibodies represented in one patient.

Table 2: All represented antibodies

Rhesus D antibody	D	41
Other-Rhesus antibodies	C	21
	c	7
	C^w	2
	E	11
	e	1
Non-Rhesus antibodies		
Kell antibodies	K	4
	K^{pa}	2
Duffy antibodies	Fy^a	5
	Fy^b	2
Kidd antibodies	Jk^a	6
	Jk^b	1
MNS antibodies	M	1
	S	1
Other antibodies	Lu^a	1

Table 3: Isoimmunizations with single and multiple antibodies

Single antibodies					
Rhesus D group	D				17
Other-Rhesus group	C				2
	c				3
	C^w				1
	E				5
	e				1
Non-Rhesus group	Jk^a				3
	Fy^a				1
	Fy^b				1
	K				2
	K^{pa}				1
Multiple antibodies					
Rhesus D group	D	+	C		13
	D	+	c		2
	D	+	E		1
	D	+	Jk^a		1
	D	+	C	+ E	1
	D	+	C	+ Jk^a	2
	D	+	C	+ Fy^a	2
	D	+	C	+ K	1
	D	+	E	+ Fy^a	1
Other-Rhesus group	c	+	E		1
	c	+	E	+ M	1
	E	+	C^w	+ S	1
Non-Rhesus group	Jk^b	+	Fy^b		1
	K	+	K^{pa}		1
	Fy^a	+	Lu^a		1

The Non-Rhesus group includes following antigens Kell (K/K^{pa}), Duffy (Fy^a/Fy^b), Kidd (Jk^a/Jk^b) and Lu^a.

Table 4: Treatment of infants with isohaemolytic disease

	Rhesus D group (n=41)	**Other-Rhesus group** (n=15)	**Non-Rhesus group** (n=11)	**p-values between Rhesus D and Other-Rhesus group**
Transfusion, n*				
Intrauterine transfusion	5	0	2	0.31
Exchange transfusion	11	0	0	0.03
Top-up red blood cell transfusion	12	0	3	0.02
Immunoglobulin, n	12	2	2	0.31
Phototherapy				
Single light, n	8	6	4	<0.001
Double light, n	33	8	7	
None, n	0	1	0	
Total duration of phototherapy, days (SD)	4.5 (2.2)	3.0 (2.5)	2.4 (0.9)	0.04
P-bilirubin levels during treatment				
Maximum p-bilirubin, µmol/L	218 (88)	214 (77)	172 (68)	0.89

* n: number of infants

Table 4 shows the different treatment types used during the period. Some of the infants have had more than one treatment, e.g. IUT, ET and/or PT. The number of infants treated with ET and top-up red blood cell transfusions were significantly higher for Rhesus D immunized infants than for other Rhesus immunized infants. The need for PT treatment with double light and total duration of PT treatment were also significantly higher for Rhesus D immunized infants than for other Rhesus immunized infants. There was no significant difference between the two groups in the maximum p-bilirubin level during treatment.

Figure 2: Rhesus D isohaemolytic disease in the period 2005-2014

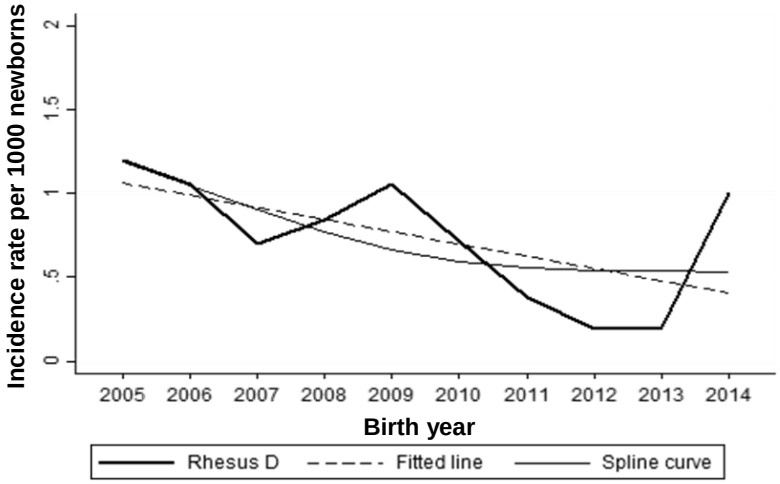


Figure 2 shows the incidence rate of newborns with Rhesus D immunization during the years 2005 to 2014. It shows a spline curve and a fitted line. For a one year increase in the birth year the incidence was on average decreased by 0.07 ‰ (95 % confidence interval -0.15 ‰ – 0.01 ‰).

A test for linearity was performed by testing if the cubic spline relationship could be reduced to a simple linear relationship (p = 0.43). Testing of the slope of the line is equal to zero: p = 0.07, i.e. there was no significant relationship between the birth year and a decreasing incidence.

Figure 3: Maximum plasma bilirubin in Rhesus D group

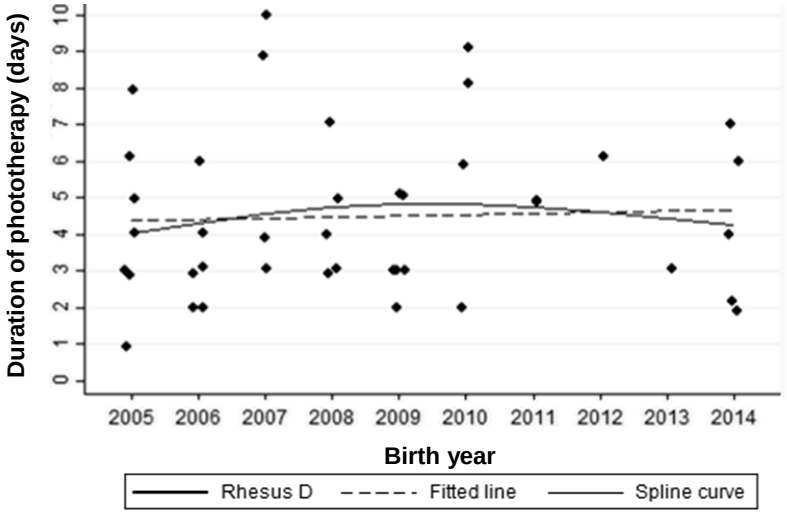
The spline curve and the fitted line are located on top of each other.

Figure 3 shows a plot of the maximum p-bilirubin in Rhesus D group during the years. A test for linearity was performed by testing if the cubic spline relationship could be reduced to a simple linear relationship (p = 0.97). For a one year increase in the birth year, the maximum plasma bilirubin for Rhesus D was on average increased by 12 µmol/L (95 % confidence interval 3 µmol/L – 21 µmol/L). Testing of the slope of the line is equal to zero: p = 0.01, i.e. there was a significant relationship between maximum p-bilirubin and the birth year.

Figure 4 shows the duration of PT treatment in Rhesus D group during the years. A test for linearity was performed by testing if the cubic spline relationship could be reduced to a simple

linear relationship (p = 0.44). Testing of the slope of the line is equal to zero: p = 0.79, i.e. there is no significant relationship between the duration of PT and the birth year.

Figure 4: Duration of phototherapy treatment in Rhesus D group



DISCUSSION

The highest rate of immunization was against Rhesus D, then Rhesus c and Rhesus E antigens. This is consistent with other studies where the prevalence of the different immunization types are studied (9,10). However a Danish study showed that the number of immunizations against Kell antigens was the second most common after Rhesus D immunizations (11).

The non-Rhesus group in this study contained immunizations against different types of antigens, with different severity of disease in which e.g. Kell is severe and Lu^a is mild (1). There were only a few number of each of these immunization types and therefore non-Rhesus groups are not discussed further in this study.

Markham et al. (12) found that women with multiple red blood cell antibodies were more likely to develop haemolytic disease of the foetus and infant than those with single antibody. Nordvall et al. (11) found that combinations of antibodies were more harmful than single antibody immunizations.

Therefore it was interesting to review the number of infants who were immunized with single and multiple antibodies. In this study 55 % of the infants were immunized with a single antibody and 45 % with multiple antibodies. The distribution of immunizations with single antibody and multiple antibodies were respectively 73% and 27 % in the first mentioned study (11) and respectively 87 % and 13 % in the other study (12). In this study the difference in severity of haemolysis with a single antibody and multiple antibodies was not examined, though this may be interesting to examine in further studies.

Gestational age, number of preterm births, birth weight and umbilical cord Hb were significantly lower in Rhesus D group compared to Other-Rhesus group and DAT was significantly higher. This shows that the infants were more affected at Rhesus D immunization than other Rhesus immunizations, which was also confirmed by a significantly higher number of infants who had had ET and top-up red blood cell transfusion. The same applies to the need for more intense PT (double light) as well as the total duration of PT. However, there was no significant difference in the number of foetuses treated with IUT. This might be due to the small population size in this study. One study found that Rhesus D immunized infants had a significantly greater need for treatment with IUT and had more severe outcome than infants with other immunizations (11). Rath et al. (13) found that there was no difference in the postnatal need for ET and top-up red blood cell transfusion when Rhesus D was compared to Rhesus c immunization. A study found that ET was independently associated with proven sepsis (14). None of the infants in our study suffered from sepsis. No significant difference between the groups was found in number of infants with IVIg treatment. In one study it was showed that IVIg reduced the need for ET (15) while in another study it was found that IVIg did not reduce the need for ET, duration of PT, maximum p-bilirubin levels and proportion of neonates who required top-up red blood cell transfusions (16).

It is interesting that there was no significant difference in the umbilical cord Hb and p-bilirubin and asphyxia between the Rhesus D and Other-Rhesus groups. This might be due to IUT treatment during pregnancy if the foetuses had threatening anaemia. IUT is theoretically associated with reduction of haemolysis and thus anaemia by replacing foetal red blood cells with from a Rhesus negative donor. Replacement should theoretically result in less active isoimmunization (8). Thus, postnatal degree of anaemia is reduced in newborns with severe disease during pregnancy which may be one of the reasons why there was no significant difference between the groups. This was confirmed in another study comparing Rhesus D immunized IUT group against non-IUT group which found a tendency that IUT treatment resulted in less active isoimmunization (8).

No significant differences were found in sex and ethnicity, although Caucasians have a higher prevalence of Rhesus D negative blood type than non-Caucasians (2).

The total incidence of isohaemolytic disease was 1.22 ‰ of which Rhesus D immunization represented 0.75 ‰. The incidence rate for the Rhesus D group had a decreasing tendency though it was not significant. This might be due to the small population size in this study. According to other studies, the incidence of Rhesus D immunizations was also declining due to introduction of antenatal anti Rhesus D prophylaxis (4,6,17,18). The incidence rate for the Other-Rhesus group was not calculated because of the small number of infants in this group.

Maximum p-bilirubin increased significantly during the observed period, while duration of treatment with PT was not, which is of interest. This may be due to a more relaxed attitude to moderate p-bilirubin levels. Characteristic clinical picture of kernicterus is extremely rare in children without a history of extreme hyperbilirubinemia. Newman and Kuzniewicz (19) provided reassurance that the risk of kernicterus among such children was low and they concluded that the

recommended PT and ET thresholds may be unnecessarily aggressive. Another reason might be a change in the ratio of double to single light towards the last one. It cannot be excluded that the increase in maximum p-bilirubin was because the infants were exposed to a decreasing dose of light during the period, though it seems unlikely because the light irradiation was determined regularly and was found to be constant.

In further studies it might be interesting to investigate the incidence of Rhesus D immunization in a major population and a greater period of time. Furthermore, this study only investigated the infants who were affected by immunization in North Denmark Region. It could be interesting to investigate all immunized mothers and follow the development of all the foetuses and newborns in this group. This could provide a better insight into the number of infants who are affected in each type of immunization as well as providing a more profound picture of the severity of the different types of immunization.

CONCLUSION

The incidence of Rhesus D immunization tended to be decreasing during the period. The maximum plasma bilirubin concentration significantly increased while the average duration of the phototherapy was constant throughout the period, probably due to less aggressive treatment.

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