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Bridging the gaps: prevention, management, and future perspectives in hemolytic disease of the fetus and newborn

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Severity of haemolytic disease of the fetus and newborn in patients with a history of intrauterine transfusions in a previous pregnancy: A nationwide retrospective cohort study

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Abstract

Objective: Pregnant women who received at least one intrauterine transfusion (IUT) for haemolytic disease of the fetus and newborn (HDFN) in the preceding pregnancy are presumed to have a high likelihood of requiring IUTs again, often starting at an earlier gestational age. Our aim was to quantify these risks in a large national cohort.

Design: Retrospective cohort study of a nationwide Dutch database.

Setting: The Netherlands.

Population: All women treated in The Netherlands with IUTs for Rhesus D (RhD)-or Kell-mediated HDFN between 1999 and 2017 and their follow-up pregnancies were included. Pregnancies with an antigen-negative fetus were excluded.

Methods: Electronic patient files were searched for the number and gestational age of each IUT, and analyzed using descriptive statistics and linear regression.

Main outcome measures: Percentage of women requiring one or more IUTs again in the subsequent pregnancy, and gestational age at first IUT in both pregnancies.

Results: Of the 321 women in our study population, 21% (69) had a subsequent ongoing pregnancy at risk. IUTs were administered in 86% (59/69) of cases. In subsequent pregnancies, the median gestational age at first IUT was 3 weeks earlier (interquartile range −6.8 to 0.4) than in the preceding pregnancy.

Conclusions: Our study shows that pregnant women with a history of IUTs in the previous pregnancy are highly likely to require IUTs again, and on average 3 weeks earlier. Clinicians need to be aware of these risks and ensure timely referral, and close surveillance from early pregnancy onwards. Additionally, for women with a history of IUT and their caregivers, this information is essential to enable adequate preconception counselling.

Introduction

Haemolytic disease of the fetus and newborn (HDFN) is generally considered to worsen with each subsequent pregnancy with an antigen-positive fetus, though there is a lack of published data.[1] A woman whose fetus required intrauterine transfusions (IUTs) to treat severe anemia is commonly told that in her next pregnancy with an antigen-positive fetus, she will not only require IUTs but the first IUT will probably be needed several weeks earlier, increasing the risk of poor outcome.[2] Our clinical experience with pregnancies involving HDFN over the past five decades confirms this high recurrence risk, however, we have observed exceptions. We found no adequately sized studies quantifying the risk of severe HDFN in pregnancies following a pregnancy in which treatment with IUTs to the fetus was necessary. The largest study to date is the PETIT study evaluating the effect of intravenous immunoglobulins (IVIg) in subsequent consecutive pregnancies with a history of severe HDFN (fetal death or IUT <24 weeks of gestation).[2] In the cohort of untreated pregnancies, all patients received IUTs in the consecutive pregnancy, 9 days earlier than the former pregnancy.[2] Evidence-based data are not only essential for adequate counselling in current daily practice, but also they may assist in decisions on who might benefit from new non-invasive treatments that are currently being developed. Immune-modulating therapies have been a focal point in addressing HDFN for decades. Among the recently developed therapies are blocking agents against the neonatal Fc receptor (FcRn), which are currently being investigated in clinical trials (NTC03842189).[1] In theory these agents possess the potential to obstruct the transmission of harmful IgG antibodies from the mother to the fetus, while also impeding their reabsorption into the maternal bloodstream. This approach is non-invasive, but highly intensive, commencing early in pregnancy to pre-empt fetal disease. If the FcRn blockers are proven to be effective, it is very important to have the capability to differentiate between those who may or may not require IUTs in a subsequent pregnancy as it would be invaluable in selecting candidates suitable for this intensive and most probably expensive therapeutic regimen.

The aim of this study was to assess the likelihood of requiring IUTs in a pregnancy, in women who received at least one IUT for HDFN in a preceding pregnancy. In addition, we assessed the gestational age at first IUT in the current pregnancy and the preceding pregnancies.

Methods

Study design and study population

We designed a retrospective cohort study using data from a previously described database.[3] The database was constructed in 2017 and comprised a cohort from 1987 until 2017. For our study we selected the cohort from 1999 onwards, because of the introduction of first-trimester screening for red blood cell (RBC) alloantibodies in all pregnant women in the Netherlands in July 1998. Before 1998, only Rhesus D (RhD) -negative women were screened for RBC alloantibodies and only around week 30 of pregnancy.[4] We selected pregnancies of women with a *first* IUT-treated pregnancy during the study period. During the study period and a follow-up period of 5 years until April 2023, we examined if there was a subsequent pregnancy. We reviewed if it concerned an antigen-positive or antigen-negative fetus.

All IUTs were performed at the Leiden University Medical Centre (LUMC), which is the national referral center for alloimmunisation in the Netherlands. Data from the LUMC were linked to data from Sanquin Diagnostic Services, the national referral laboratory for diagnostic follow up for pregnancies complicated by RBC alloantibodies.[3] By combining these two national databases, a nationwide cohort was created and no alloimmunised pregnancies were missed. Women who had IUTs for severe HDFN are almost always referred to the LUMC early in the next pregnancy. When the father is homozygous for the antigen in question, the fetus is assumed to be antigen-positive and hence at risk for developing HDFN. In the case of a heterozygous father, fetal blood group genotyping used to be done by amniocentesis, replaced since 2004 by non-invasive cell-free DNA testing.[5] If the fetus is typed as antigen negative, then the pregnant woman is referred back to her own local hospital. For all women in the cohort, we checked in the database of Sanquin whether testing was performed for pregnancies that may not have had an early referral to LUMC.

We only selected RhD- and K(ell)- mediated HDFN cases as these antibodies comprise the vast majority (92-97%) of severe HDFN cases.[6-7]

Antenatal management and intrauterine transfusion techniques

We previously described antenatal management and transfusion techniques of this cohort.[3] In summary, weekly ultrasound scans are performed, and if the peak systolic flow of the middle cerebral artery exceeds 1.55 times the multiples of the mean, or if there are signs of anemia such as hydrops, ascites, or cardiomegaly, the decision is made to perform fetal blood sampling followed by an IUT. These transfusions are

almost exclusively performed in the intrahepatic part of the umbilical vein in the fetus, with or without an intraperitoneal deposition, or transplacentally at the cord root. This management strategy does not differ between the initial immunized pregnancies necessitating transfusions and subsequent pregnancies. During the study period, the only change in management that could affect the need for transfusions was the introduction of IVIg in our center in about 2010. IVIg is offered to women with a very severe obstetric history, defined as transfusions in a previous pregnancy before 24 weeks of gestation or a previous fetal or neonatal death due to HDFN.

Data collection

Data collected in the previously described database included obstetric characteristics such as gravidity, IVIg administration, number of IUTs, antibody titers, antibody-dependent cellular cytotoxicity (ADCC) levels and hemoglobin levels before and after IUT, as well as neonatal characteristics such as hemoglobin levels at birth, and need for phototherapy and exchange transfusions.[3]

Outcome measures

The primary outcome was the percentage of women with one previous pregnancy with IUT treatment for HDFN that needed IUT treatment in the subsequent pregnancy with an antigen-positive fetus. Secondary outcomes were the difference between gestational age at IUT in first and subsequent IUT treated pregnancy, and the number of IUTs needed. A core outcome set was not used for the design of this study as no core outcome set exists yet for HDFN.

Statistics

The outcome measures were analyzed using descriptive statistics. Linear regression was used to predict the expected gestational age at IUT in a follow-up pregnancy as a function of gestational age at IUT in the first pregnancy. In this analysis the residual standard deviation (SD) was assumed to increase with increasing gestational age, because this better fitted the data. When no IUT was performed in the following pregnancy, the gestational age at birth was used as outcome in the regression analysis.

Ethical considerations

The medical ethics committee of the LUMC (C15.094) approved this study.[3] The data that support the findings of this study are available on request. The data are not publicly available because of privacy and ethical restrictions.

Results

In our cohort between 1999 and 2017, 321 women had a first pregnancy treated with IUTs for RhD- or K-mediated HDFN. Of these women, 74/321 (23%) had a known subsequent pregnancy with an antigen-positive fetus. Five pregnancies were excluded for intrauterine fetal demise before the first IUT (n=1), miscarriage or abortion (n=3) or participation in a trial studying a new non-invasive treatment for severe HDFN (NTC03842189) that could alter the outcome (n=1). In 86% (59/69) of the included women, IUTs were needed again in the subsequent pregnancy (Figure 1).

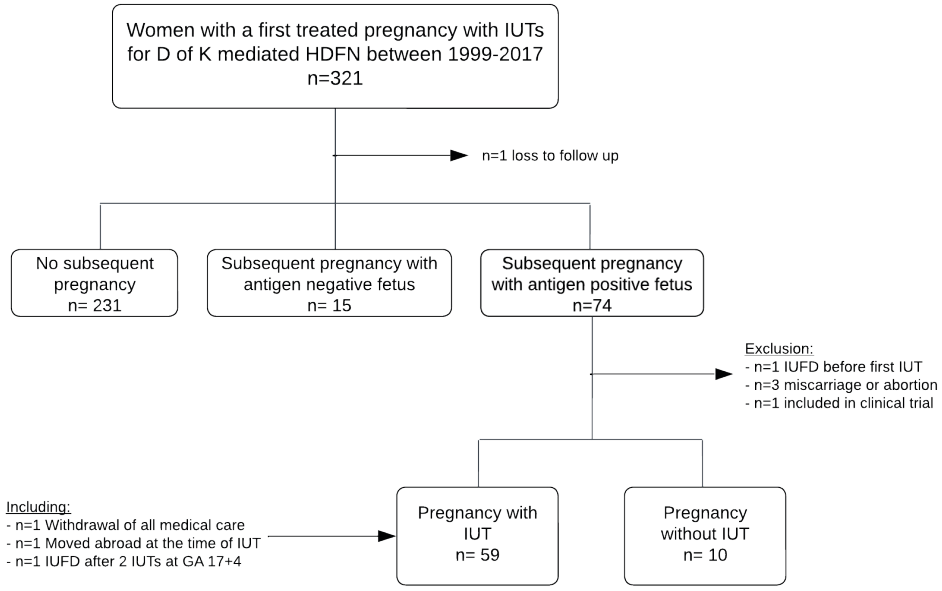

Figure 1. All women with a first treated pregnancy with IUTs for RhD or K mediated HDFN and their subsequent pregnancies with an antigen positive fetus were included. The women pregnant of a negative fetus or who did not have a subsequent pregnancy were depicted separately. On woman resides in Belgium and after her initial pregnancy was loss to follow-up. In the group of women with a subsequent pregnancy with IUTs there was one case in which a women withdrew from all medical care when IUT treatment was needed and advised. Another women migrated to France and it was advised to get IUT treatment there. Finally in one pregnancy two IUTs were administered after which the fetus died. IUT: intrauterine transfusion, HDFN: Hemolytic Disease of the Fetus and Newborn, IUFD: Intrauterine Fetal Demise, GA: gestational age.

The characteristics of the first IUT-treated pregnancies of all 321 women are presented in Table 1, and separately for the first IUT-treated pregnancy of women with a subsequent pregnancy with and without IUTs.

Table 1. Characteristics of the first IUT-treated pregnancies.

		First pregnancy of women with:	
	All first pregnancies with IUT (n=321)	**Subsequent pregnancy with IUT (n=59)**	**Subsequent pregnancy without IUT (n=10)**
Maternal age at first IUT (years)	32 (18-43)	29 (19-39)	29 (22-37)
Gravidity	3 (1-13)	3 (1-9)	3 (2-5)
Type of alloimmunisation			
RhD	262† (82)	54 (92)	10 (100)
K (Kell)	60† (18)	5 (8)	
Max titer	256 (4-16000)	256 (4-8000)	512 (128-1000)
GA at first IUT, (weeks)	28 (16-35)	28 (16-35)	32 (25-34)
Number of IUTs	3 (1-6)	3 (1-6)	2 (1-3)
ZHb	-7 (-12 to -1)	-7 (-10 to -2)	-6 (-8 to -2)
Hydrops			
No	268 (84)	53 (90)	10 (100)
Mild	39 (12)	5 (8)	
Severe	14 (4)	1 (2)	
GA at birth	37 (19-39)	37 (22-38)	37 (35-38)
Survival			10 (100)
Yes	314 (98)	55 (93)	
Antepartum demise	5 (1.5)	4 (7)	
Postpartum demise	2 (0.5)	0 (0)	

Note: Data presented as median (range) or as number (%).
Abbreviations: GA, gestational age; IUT, intrauterine transfusion; RhD, Rhesus D.
[a]Adds up to more than the number of pregnancies, one pregnancy was affected by both RhD and Kell.
Zhb is the number of standard deviations from the mean concentration for gestational age.[7]

The majority of pregnancies were complicated by RhD antibodies (82%), in the subgroups with and without IUTs in subsequent pregnancy this was 91% and 100%, respectively. In the subgroup with a subsequent pregnancy with IUTs, the median gestational age at the first IUT in the previous pregnancy was 28 weeks (range 16-35) whereas in the women with a subsequent pregnancy without IUTs this was 32 weeks (range 25-34 weeks). In the group with IUTs in their subsequent pregnancy, three IUTs were needed in the first IUT-treated pregnancy (range one to six versus two; range one to three) and 10% of the fetuses experienced hydrops, compared with 0% in the group of women without IUTs in their subsequent pregnancy. The survival rate in the group with subsequent IUTs was 93% in comparison with 100% of the women without IUTs in their subsequent pregnancy. Additionally, all anti-K-mediated HDFN pregnancies with a subsequent pregnancy required IUTs again.

Interval in gestational age at first IUT in first and second IUT-treated pregnancies

In the subsequent pregnancy, 60% (n=41) of women received their first IUT earlier, 25% had their first IUT later (n=1 at the same gestational age, n=16 later) and 15% (n=10) did not need IUTs. There is one missing value of a woman who withdrew from all medical care at the time IUTs were planned and needed (Figure 1). Pregnancies in which IUTs were needed again had a median gestational age at the first IUT of 24 weeks (range 16-34 weeks), a median of 3 weeks (interquartile range [IQR] -6.8 to 0.4) earlier than in the previous pregnancy. In subsequent pregnancies, seven women were treated with IVIg, and all of them had IUTs again. The median interval did not change when the analysis was repeated without the IVIg-treated women.

Figure 2 outlines a first start at designing a predictive model for anticipating the timeframe in the subsequent pregnancy when IUTs would be needed again. The individual data of gestational age at first IUT in the first and second IUT-treated pregnancies is given, with the expected gestational age at IUT in the second pregnancy for a given value of the gestational age at first IUT. For women without an IUT in their subsequent pregnancy, gestational age at birth of the second pregnancy is depicted. The dotted line corresponds to the $x = y$ reference line denoting an absence of disparity in gestational age. The solid lines depict the mean reference values (mean ± 2 SDs) for the expected gestational in a subsequent pregnancy, based on our cohort. It additionally shows that the interval is smaller when IUTs are needed earlier in the first pregnancy and this interval gets larger when IUTs are required later in pregnancy.

Subsequent pregnancy without IUTs

Maternal and fetal characteristics of the first pregnancy with IUTs of the subgroup of women with a subsequent pregnancy without IUTs are displayed in Table 2.

The majority had their first IUT in the previous pregnancy at or after 30 weeks of gestation. The absolute hemoglobin values before the first IUT had a median of 7.8 g/dL (IQR 6.9- 9.0); for nine out of ten of the fetuses, the hemoglobin level was more than 3 SDs below the mean level for gestational age, (IQR -7.0 to -4.0). The maximum titer ranged between 128 and 1000 and the ADCC[8] had haemolytic activity levels of at least 50% in all pregnancies. It is worth noticing that after reaching this guideline advised cut-off value for pregnancies at high risk, laboratory testing was not always continued. Patients are referred to the Leiden University Medical Centre as this is the national referral center. Patients are followed weekly, and management is solely based on ultrasound measurements.

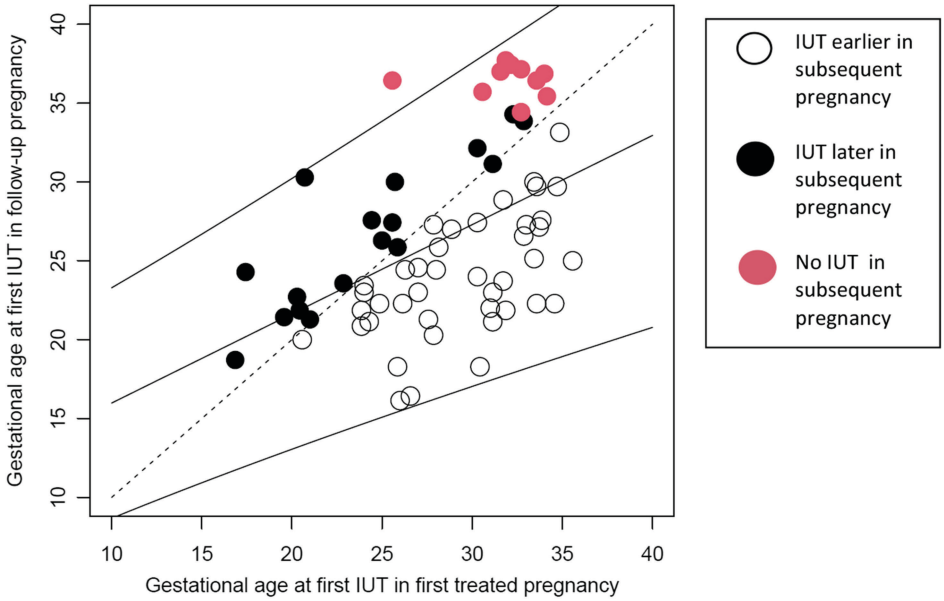

Figure 2. Relationship between gestational age at first IUT in first and second treated pregnancies. Data of all women who had a second pregnancy with an antigen-positive fetus after a pregnancy complicated by IUT(s). Black circles represent women with IUTs in the subsequent pregnancy, solid circles for the women with an IUT at a later gestational age in the next pregnancy and open circles for women with an IUT at an earlier gestational age in the subsequent pregnancy. Red circles represent the women without IUTs in the subsequent pregnancy. For these women the gestational age at delivery was used as gestational age at first IUT in the second pregnancy. The lines plotted represent the expected mean gestational age ± 2 standard deviations, and the dashed line represents the x = y function, i.e. IUT in both pregnancies will take place at the same gestational age. IUT, intrauterine transfusion.

Table 2. Obstetric characteristics of the first IUT-treated pregnancy of the ten women with a subsequent pregnancy without IUT(s).

	GA at first IUT (weeks)	Number of IUTs	Hb before first IUT (g/dL)	Zhb†	Highest titer	Highest ADCC (%)
Patient 1	31	2	7.7	-6.2	128	90
Patient 2	25	2	8.4	-4.4	512	90
Patient 3	32	2	7.1	-7.0	256	90
Patient 4	34	1	8.2	-6.2	256	80
Patient 5	32	2	12.2	-1.8	512	70
Patient 6	34	1	7.1	-7.3	512	65
Patient 7	30	3	7.9	-5.8	512	90
Patient 8	33	1	5.9	-8.3	512	90
Patient 9	32	2	10.8	-3.3	128	50
Patient 10	31	2	6.3	-7.7	1000	90

Note: Obstetric characteristics of the first IUT-treated pregnancies of women who had a subsequent pregnancy without IUTs. All alloimmunizations were caused by anti-D.
Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; GA, gestational age; Hb, hemoglobin; IUT, intrauterine transfusion.
[a]Zhb is the number of standard deviations from the mean concentration for gestational age.[7]

The characteristics of the subsequent pregnancies without IUTs are outlined in Table S1. Two pregnancies were cases of twins, and one of these cases was completely monitored in a regional hospital, because cut-off values to refer to the LUMC were not reached (patient 9). In all pregnancies the partners were homozygous positive for the RhD antigen, and there were only two women with a new partner in the subsequent pregnancy. None of these women received IVIg.

All but two of the neonates were born anemic. All neonates required phototherapy, which is given prophylactically after a pregnancy complicated by alloantibodies. A third of the neonates (4/11) also required an exchange transfusion, and two neonates required at least one additional simple transfusion. Standard of care for these high-risk pregnancies is delivery in the LUMC and an induction of labor between 37 and 38 weeks of gestation. Between 35 and 37 weeks, if severe fetal anemia is suspected, preterm labor is induced because the associated risks of conducting IUTs outweigh the benefits compared with managing the condition outside the uterus and the potential onset of preterm labor. One woman in our cohort had signs of pre-eclampsia and was hospitalized in her regional hospital. She was pregnant with twins and one of the fetuses showed signs of anemia. Because of the pre-eclampsia and the suspected anemia, the delivery was induced and the preterm delivery took place in the regional hospital.

Discussion

Main findings

This is the first study reporting the course of HDFN in a pregnancy at risk after a pregnancy treated with IUTs. We found that treatment with IUT in the subsequent pregnancy was required in the vast majority of pregnancies (86%). In 60%, the IUTs were started significantly earlier that in the previous pregnancy. In subsequent pregnancies without the need for IUT, delivery was often induced preterm, and babies born in this group had low hemoglobin levels, indicating that a longer duration of pregnancy could have made IUT treatment necessary.

In subsequent pregnancies, when IUTs were needed again, the first IUT occurred a median of 3 weeks earlier than the first IUT in the previous pregnancy; however, the range was quite large. This earlier need for IUTs in subsequent pregnancies is comparable to international data.[2] An international multicenter study on the effect of IVIG on the onset of severe fetal anemia in women with a history of severe fetal anemia found an interval of 9 days in the non-treated group.[2]

Strengths and limitations

A strength of this study is the composition of the cohort, for which data of all pregnant women in the Netherlands (currently about 170 000 a year) can be used, because the tertiary level of care to alloimmunised women is centralized. In addition, the follow-up screening is nearly complete (99.9%).[9] This creates a large uniformly treated cohort. A limitation in this study is that due to the design of the study, women who may have had pregnancies outside the Netherlands would be missed, but we expect that this concerns a limited number. Furthermore, early miscarriages before RBC alloantibody screening or before a first visit at our tertiary care center could also be missed, but as we expect that the risk on non-alloimmune-related miscarriages will not be different between pregnancies with and without a subsequent need for IUT, this would not affect the results and conclusions of our study.

To construct a predictive model for identifying individuals who might require a transfusion in their subsequent pregnancies our sample size is still too small. Hydrops, titer, ADCC, antibody specificities, subclass and glycosylation are all possible factors that could be used in this model. To further improve the care for such a rare condition, the establishment of a multicenter international registry is mandatory. We recently started such an international collaboration within the DIONYSUS registration study.[10]

Interpretation

Women who experienced a pregnancy with severe HDFN, requiring IUTs, are often told that a subsequent pregnancy, with again an antigen-positive fetus, may be extremely hazardous, with a high risk of adverse outcome. They often perceive this as advice to refrain from having another child. We have shown that indeed the vast majority require IUTs again, and often starting several weeks earlier than in the previous pregnancy. Previously we have also shown that outcomes are generally good.[7] Interestingly, in 25% of women, the first IUT in the subsequent pregnancy was at a later gestational age compared with the previous pregnancy, and, although exceptionally, some did not need IUTs at all.

Multiple factors have been described influencing the severity of HDFN. IgG-Fc glycosylation patterns of RhD and K antibodies have been described to influence severity of disease.[11-12] Low fucosylated antibodies may cause more severe HDFN and although antibody profiles do not seem to change between pregnancies, minor changes may be of influence. However, even more intriguingly, there appears to exist an immunological

memory associated with these profiles.[12] Another factor not extensively analyzed yet is the contribution of the IgG-Fc-receptor type IIIa polymorphism to disease severity. We previously reported that a higher rate of high-affinity FcγR alleles (*FCGR3A-158V*) was found in fetuses with severe HDFN.[13] Finally, unexpected mild disease could also result from the formation of monocyte-reactive IgG alloantibodies with HLA-DR specificity that are capable of blocking FcR-mediated functions, thereby inhibiting the destruction of alloantibody-loaded red cells.[14-15] In the 1990s it was demonstrated that some women formed these antibodies, which led to unexpectedly mild disease in their subsequent child after a previous, more severe case. Unfortunately, we could not retrieve materials from these pregnancies to test this theory on our cohort.

The favorable outcome in most subsequent pregnancies is only reached however upon early referral, and frequent, best weekly, careful surveillance in an experienced fetal medicine center. Since some of the IUTs needed to be performed before 20 weeks of gestation, a highly experienced fetal therapy team is a prerequisite for good outcome. Even in the best centers, the risk of fetal demise in IUTs performed before 22 weeks is as high as 20%.[16]

In pregnancies with HDFN and a previous pregnancy requiring IUT before 24 weeks of gestation, IVIg can be considered because it may aid in postponing the first IUT.[2,7] Our study provides additional evidence to support who should be considered for IVIg or new immunomodulatory agents, such as FcRn-targeted inhibitors. The latter, to preclude the need for IUT, are currently investigated.[17-18]

Conclusion

To conclude, 86% of women with a history of IUTs were in need of one or more IUTs in a subsequent pregnancy, and often IUT therapy started several weeks earlier. Still, with early, frequent surveillance in an experienced fetal therapy center, most women eventually took home a healthy baby.

Acknowledgements

We thank Peter Kooyman and Eline van Lierop-Kwast, department of Immunohematology Diagnostics, Sanquin Diagnostic Service for their help with data collection and retrieval.

Details of ethical approval

A waiver of consent was obtained from the medical ethics committee of the LUMC (C15.094) and it was concluded that written informed consent was not needed. From 2017 onward, all women who receive intrauterine treatment in the LUMC are asked prospectively for consent to use their data for study related purposes. Thus, the extra data collected from this moment onward for this study was all with consent of the participants

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Supplemental material

Table S1. Characteristics in the subsequent immunized pregnancies without IUTs of the 10 women with a foregoing pregnancy with IUTs.

	New partner	Zygosity	Highest Titer	Highest ADCC (%)	GA at birth	Hb (g/dL) at birth	ET	ST†	PT
Patient 1	Yes	Homozygous D	128	65	37+0	19.3	No	No	Yes
Patient 2	No	Homozygous D	512	90	36+3	8.5	Yes	Yes	Yes
Patient 3‡	No	Homozygous D	64	40	34+3	UNK	UNK	UNK	UNK
Patient 4	No	Homozygous D	256	90	36+6	14.5	Yes	No	Yes
Patient 5	No	Homozygous D	32	90	37+3	11.8	No	No	Yes
Patient 6	No	Homozygous D	512	50	35+3	10.6	No	No	Yes
Patient 7	No	Homozygous D	64	50	35+5	9.2	Yes	No	Yes
Patient 8	No	Homozygous D	128	90	36+3	4.4	Yes	UNK	Yes
Patient 9‡	No	Homozygous D	256	35	37+1	18.3 11.6	No No	No Yes	Yes Yes
Patient 10	Yes	Homozygous D	128	55	37+5	14.7	No	No	Yes

Characteristics of the subsequent pregnancies without IUTs of women who had a foregoing pregnancy with IUTs for HDFN. † Only simple transfusions administered in the period directly after birth, during hospitalization at the LUMC is known and displayed. ‡Patient 3 and 9 both carried twins. Patient 3 delivered at a regional hospital. Only gestational age at birth is known. Patient 9 was monitored during her entire pregnancy in a regional hospital. IUT: intrauterine transfusion; HDFN: haemolytic disease of the fetus and newborn; GA: gestational age; Hb: hemoglobin; ET: exchange transfusion; PT: phototherapy; ST: simple transfusion.