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Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures

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KEYWORDS: fetal anemia; intrauterine blood transfusion; perinatal loss; procedure-related complication; red-cell alloimmunization in pregnancy

ABSTRACT

Objective *Maternal alloimmunization to fetal red-blood-cell antigens is a major cause of fetal anemia, which can lead to hydrops and perinatal death if untreated. The cornerstone of management during pregnancy is intrauterine intravascular blood transfusion (IUT). Although this procedure is considered relatively safe, complications continue to occur. The aim of this study was to evaluate rates of procedure-related complications and perinatal loss following IUT, and their change over time, in order to identify factors leading to improved outcome.*

Methods *This was a retrospective analysis of all IUTs for red-cell alloimmunization performed at the national referral center for fetal therapy in The Netherlands, from 1988 to 2015. Differences in complication rates and their associations with alterations in transfusion technique after 2001 were assessed.*

Results *Between 1988 and 2015, 1678 IUTs were performed in 589 fetuses. For IUTs performed in 2001 and onwards, there was significant improvement in survival (88.6% vs 97.0%, P < 0.001) and a decline in procedure-related complications per fetus (9.8% vs 3.3%, P = 0.001) and per procedure (3.4% vs 1.2%, P = 0.003) compared with those performed before 2001. Procedure-related perinatal loss declined from 4.7% to 1.8% per fetus (P = 0.053). Beneficial changes in transfusion technique were routine use of fetal paralysis, increased use of intrahepatic transfusion and avoidance of arterial puncture.*

Conclusions *IUT has become an increasingly safe procedure in recent years when performed by experienced hands. The chosen technique should be fine-tuned according to the patient's individual situation. The declining complication rates are most likely related to center volume: this rare procedure is best performed in experienced fetal therapy centers.* © *2016 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Since its introduction in 1981, intrauterine intravascular blood transfusion (IUT) has become the cornerstone of treatment for fetal anemia in pregnancies complicated by red-cell alloimmunization[1]. In experienced hands, it is nowadays considered a safe procedure, significantly improving perinatal outcome in fetuses with severe anemia[2,3].

One way to improve fetal outcome further is to minimize the occurrence of procedure-related (PR) complications associated with IUT. A PR fetal-loss rate of approximately 2% per procedure was reported in a review by Schumacher and Moise[4]. However, the small studies included in their review used a variety of definitions for complications and treatment techniques. In 2005, we reported PR complications and fetal-loss rates of 3.1% and 1.6% per procedure, respectively, in a single-center series of 740 IUTs[5]. In our study, transamniotic 'free loop' needling, inadvertent arterial puncture and refraining from the use of fetal paralysis were identified as risk factors for adverse outcome[5]. Apart from the technical aspects, operator and team experience are known to be of utmost importance for performing successful and safe IUTs [6]. In recent years, a few smaller studies have been performed on this subject,

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revealing no relevant new insights or tools to improve perinatal outcome further after IUT[7,8].

The present study aimed to evaluate PR complications and perinatal loss rates after IUT, including assessment of their change over time, over a period of nearly three decades in a national single-center cohort, in order to identify factors leading to improved outcome.

METHODS

Patients

We included all patients treated with IUT between January 1988 and January 2015 at the national referral center for fetal therapy in Leiden, The Netherlands, for fetal anemia caused by red-blood-cell alloimmunization. The findings of IUTs performed between 1988 and 2001 have been analyzed and published previously[5].

Patient data, technical aspects of IUT and complications were collected from our custom-built electronic Rhesus database. As early IUT is known to be associated with higher perinatal loss rates[9–12], we compared outcomes after IUTs performed before and after 20 weeks' gestation to determine whether expected improvements in survival also apply to very young anemic fetuses. To identify changes in procedural techniques and perinatal outcome, pregnancies were divided into two cohorts according to year of procedure. The first cohort included patients with a first IUT before January 2001, described previously[5], and the second cohort included patients with a first IUT performed from 1 January 2001 onwards. This policy was chosen as it was assumed that the findings of our first study in 2005[5] may have resulted in gradual changes in transfusion techniques and therefore also in perinatal survival.

Complications after IUT were classified independently into PR or non-procedure related (NPR)[5] by two operators (I.L.v.K. and D.O.). In summary, fetal condition before IUT was assessed by ultrasound (presence of hydrops, biophysical profile), fetal heart rate tracing in fetuses > 26 weeks' gestation and blood gas analysis of the fetal blood sample obtained before transfusion (a blood pH of ≤ 7.25 was considered a sign of fetal compromise)[5]. If a complication occurred during or after a complicated procedure in a fetus with a reasonable condition prior to IUT based on the abovementioned findings, the complication was considered to be related to the procedure i.e. PR. In fetuses with an unfavorable condition prior to an uncomplicated procedure, the complication was classified as not related to the procedure i.e. NPR. If the experts could not agree on classification, the complication remained unclassified.

The following complications were taken into account: rupture of membranes or preterm delivery within 7 days after IUT, if occurring before 34 weeks of gestation; and intrauterine infection and fetal distress resulting in either emergency Cesarean section (CS) within 24 h after IUT or fetal or neonatal death.

Primary outcomes assessed were perinatal survival and PR complications. Furthermore, we assessed primary antibody type, gestational age at first IUT, fetal hemoglobin concentration and presence of hydrops at first IUT, procedure access site and other technical details of IUT, number of transfusions per fetus and gestational age at delivery.

Diagnostics

Patients with red-cell alloimmunization were referred, according to national guidelines, to our center in Leiden, The Netherlands, which has served as the national referral center for fetal therapy since 1965. Indication for referral is based on type and titer of antibody, level of antibody-dependent cell-mediated cytotoxicity assay[13] and obstetric history.

In the first decade of the study period, amniotic fluid delta optical density measurements at 450 nm were used to assess the likelihood of fetal anemia. In later years, the peak systolic velocity in the fetal middle cerebral artery (MCA-PSV) was used to determine the optimal timing of first and subsequent IUTs[14–16]. Cordocentesis was performed if MCA-PSV exceeded 1.5 multiples of the median and/or if signs of hydrops were detected on ultrasound, and was followed by transfusion if the fetal blood sample showed fetal anemia.

Intrauterine intravascular blood transfusion technique

Our IUT technique has been described comprehensively in a previous publication[3]. No routine antibiotic prophylaxis or corticosteroid was administered prior to IUT. In nearly all recent cases, atracurium was given intravenously (or intramuscularly) to the fetus prior to transfusion to cause fetal paralysis.

IUT was carried out under aseptic conditions, using a 20- or 22-G needle. In this study, all IUT attempts were made intravascularly. As a result of our prior study[5], fetal paralysis was applied more often and known risk factors for PR complications, such as transamniotic needling (also known as 'free loop' needling) and arterial puncture, were avoided more consciously in the second half of the study. A tailored mode of transfusion was chosen depending on the fetal anatomy, preferably transfusing into the placental cord insertion in the case of an anterior placenta and into the fetal intrahepatic umbilical vein in the case of a posterior placenta, often in combination with additional intraperitoneal transfusion. For both time cohorts, a maximum of four experienced operators were involved, all capable of applying different transfusion techniques. IUT was considered to be successful if more blood than was acquired for fetal blood sampling was transfused to the fetus, as verified by ultrasound.

Fetal condition was monitored before, during and after transfusion. If the condition of the mother and fetus was satisfactory, patients were discharged within 6 h after IUT.

Statistical analysis

To compare proportions, Fisher's exact test (or Pearson's chi-square test, when appropriate), binary logistic

Table 1 Characteristics of 1678 intrauterine intravascular blood transfusions (IUTs) in 589 fetuses with anemia caused by red-cell alloimmunization, according to study period in which procedure was performed

Characteristic	*1988–2000 (n = 255 fetuses/741 IUTs)*	*2001–2015 (n = 334 fetuses/937 IUTs)*	P
Primary immunization against:			
Rhesus D	217 (85.1)	255 (76.3)	0.009
Kell	25 (9.8)	53 (15.9)	0.037
Other*	13 (5.1)	26 (7.8)	0.242
GA at first IUT (weeks)	27 (17 to 36)	27 (16 to 35)	0.787
Hydrops at first IUT	97 (38.0)	43 (12.9)	< 0.001
Hemoglobin at first IUT (g/dL)	4.8 (1.1 to 13.2)	6.3 (1.5 to 12.9)	< 0.001
Z-hemoglobin at first IUT†	−8.3 (−12.2 to −0.24)	−6.9 (−11.7 to −0.5)	<0.001
Δ Hemoglobin (after IUT − before IUT) (g/dL)	4.5 (−0.5 to 11.2)	4.4 (0.5 to 9.2)	0.039
Number of IUTs per fetus	3 (1 to 7)	3 (1 to 6)	0.337
GA at delivery of liveborn (weeks)	37 (30 to 39)	36 (28 to 39)	< 0.001

Data are given as *n* (%) or median (range). *Rhesus c, E or e, Duffy (Fya), Kidd (Jka), rare or low-frequency antigens. †Number of SDs from median concentration for gestational age. GA, gestational age.

regression (Wald test) or Mann–Whitney *U*-test was used. The independent *t*-test was used for comparison of means. All variables with *P*-value of ≤ 0.15 in univariate analysis were included in a multiple logistic regression model to identify possible independent risk factors for severe PR complications (emergency CS or death). A *P*-value of < 0.05 was considered statistically significant.

RESULTS

During the 27-year study period, 595 fetuses in 587 pregnancies of 497 women received a total of 1685 IUTs, of which 740 were described previously[5]. In eight twin pregnancies, both twins had anemia as a result of red-cell immunization and received IUTs. In one additional twin pregnancy, one fetus was affected and was included in this study; the cotwin was Rhesus D (RhD) negative. Six singleton pregnancies, in which fetal death occurred from causes unrelated to red-cell alloimmunization, were excluded, as described in detail previously[5]. Therefore, 589 fetuses were treated with a total of 1678 IUTs in 581 pregnancies of 491 women. Of these, 741 procedures were performed in 255 fetuses before 2001 and 937 procedures were performed in 334 fetuses from 2001 onwards.

Overall perinatal survival was 93.4%, significantly increasing from 88.6% in the first time-cohort to 97.0% in the second time-cohort (odds ratio (OR), 4.2 (95% CI, 2.0–8.7), $P < 0.001$). Characteristics of the study population in both time-cohorts are summarized in Table 1. The main type of immunization was for RhD, although this significantly decreased from 85.1% before 2001 to 76.3% from 2001 onwards ($P = 0.009$), whereas the proportion of Kell immunization increased (9.8% to 15.9%, $P = 0.037$, Table 1). In the second time-cohort, four patients were treated with intravenous immunoglobulin prior to the first transfusion.

Complications

In a total of 1678 IUTs, 69 complications occurred. Forty-four of these were considered as being directly related to the procedure (PR). In eight patients, one PR complication led to another (five emergency CSs followed by perinatal death, two intrauterine infections followed by perinatal death and one intrauterine infection followed by emergency CS). After correction for this, the actual PR complication rates for the total cohort over 27 years were 6.1% per fetus and 2.1% per procedure. Survival and PR complications are listed in Table 2.

In the first time-cohort, there were 51 complications (seven women each had two complications; actual complication rate = 5.9% per procedure) and in the second time-cohort there were 18 (one women had two complications; actual complication rate = 1.7% per procedure) ($P < 0.001$). Compared with the first cohort, the incidence of PR complications significantly declined in the second cohort, from 9.8% to 3.3% per fetus (OR, 0.3 (95% CI, 0.2–0.7), $P = 0.001$) and from 3.4% to 1.2% per procedure (OR, 0.3 (95% CI, 0.2–0.7), $P = 0.003$). The risk of PR perinatal loss decreased over time from 4.7% to 1.8% per fetus and from 1.6% to 0.6% per procedure (Table 2).

Preterm prelabor rupture of membranes and preterm delivery

In three cases, preterm prelabor rupture of membranes (PPROM) occurred within 7 days after transfusion, leading to preterm delivery before 34 weeks. One PR and one NPR classified PPROM are described in more detail in our previously published cohort study[5]. In the second time-cohort, PPROM occurred in one case, the day after the first IUT at 30 weeks' gestation. The baby was liveborn 8 days later. As it took three attempts to complete the transfusion successfully, this complication was classified as PR. The PR-PPROM rate was thus low in both cohorts and did not differ significantly (Table 2).

Infection

Three cases of culture-proven intrauterine infection with *Escherichia coli* were observed, and all three were classified as PR. Two cases were part of our previously

Table 2 Outcome and procedure-related complications after 1678 intrauterine intravascular blood transfusions (IUTs) in 589 fetuses with anemia caused by red-cell alloimmunization, according to study period in which procedure was performed

Outcome	*1988–2000 (n = 255 fetuses/ 741 IUTs)*	*2001–2015 (n = 334 fetuses/ 937 IUTs)*	*OR (95% CI)*	P
Survival (*n* (%))*	226 (88.6)	324 (97.0)	4.16 (2.0–8.7)	< 0.001
Procedure-related complication (*n*)	32	12		
Per fetus (*n* (%))†	25 (9.8)	11 (3.3)	0.31 (0.2–0.7)	0.001
Per procedure (*n* (%))†	25 (3.4)	11 (1.2)	0.34 (0.2–0.7)	0.003
Procedure-related PPROM (*n*)	1	1		
Per fetus (%)	0.4	0.3	0.76 (0.0–12.3)	1.000
Per procedure (%)	0.1	0.1	0.79 (0.0–12.7)	1.000
Procedure-related infection (*n*)	2	1		
Per fetus (%)	0.8	0.3	0.38 (0.0–4.2)	0.581
Per procedure (%)	0.3	0.1	0.40 (0.0–4.4)	0.587
Procedure-related emergency CS (*n*)	17	4		
Per fetus (%)	6.7	1.2	0.17 (0.1–0.5)	< 0.001
Per procedure (%)	2.3	0.4	0.18 (0.1–0.5)	< 0.001
Procedure-related loss (*n*)	12	6		
Per fetus (%)	4.7	1.8	0.37 (0.1–1.0)	0.053
Per procedure (%)	1.6	0.6	0.39 (0.1–1.0)	0.059

*Alive at discharge from tertiary center. †Actual number and rate (eight patients had two interrelated complications). CS, Cesarean section; OR, odds ratio; PPROM, preterm prelabor rupture of membranes.

published cohort with IUTs before 2001[5]. A third case occurred in the second cohort after IUT at 18 weeks. The infection led to fetal loss and was considered to be PR. The decrease in PR infections over time, from 0.8% to 0.3% per fetus and from 0.3% to 0.1% per procedure, was not significant (Table 2).

Emergency Cesarean section

Within 24 h after IUT, 24 fetuses were delivered by emergency CS for fetal distress, which was considered PR in 21 cases. Five children died subsequently; all deaths were PR and have been described previously[5]. As fetal condition in two of the six cases in the second cohort was unfavorable prior to an uncomplicated IUT, these complications were considered NPR. One case of PR intrauterine infection resulted in emergency CS[5]. In one case, emergency CS was performed at 34 weeks' gestation for persistent tachycardia after transfusion, probably triggered by volume overload, and was considered as PR. The three remaining cases of CS at 32, 34 and 35 weeks were all classified as PR. All neonates in the second cohort survived after emergency CS. In summary, the occurrence of PR emergency CS decreased from 6.7% in the first cohort to 1.2% in the second cohort ($P < 0.001$) and from 2.3% to 0.4% per procedure ($P < 0.001$).

Fetal or neonatal death

During the study period, a total of 39 cases of fetal or neonatal death occurred after IUT, of which 10 occurred from 2001 onwards. In this second cohort, one patient with RhD immunization was treated initially with (a possibly incomplete) interstitial laser for twin reversed arterial perfusion syndrome and fetal death was detected the day after the third uncomplicated IUT. Because of the complexity of this case, this complication could not be clearly classified as PR or NPR. Three of the nine remaining cases of loss were considered to be NPR. One NPR loss occurred after the decision to stop intrauterine treatment, as a result of refractory severe hydrops that was diagnosed relatively late and was caused by antibodies against a low-frequency antigen. In the two other cases, fetal death was detected 19 and 22 days after an uncomplicated IUT and, because of the time lapse between the procedure and the death, these deaths were considered as being NPR.

Therefore, a total of six PR losses occurred in the second cohort, including one with *E. coli* infection that was described earlier. In three patients, multiple attempts at intravenous access led to bradycardia during the procedure, leading to fetal loss directly, and at 1 and 8 days later. Two other PR fetal losses occurred within 1 week after IUTs at 16 and 26 weeks in fetuses with a reasonable condition prior to IUT. We thus saw a decrease in PR death rates from 4.7% to 1.8% per fetus ($P = 0.053$) and from 1.6% to 0.6% per procedure ($P = 0.059$).

Fetal death occurred after eight (17.0%) of 47 IUTs performed before 20 weeks. Four of these were classified as NPR and four as PR, one of the latter was preceded by infection. Fetal demise in the total cohort occurred more often before 20 weeks than after 20 weeks, accounting for both NPR (8.5% *vs* 1.0% per procedure; $P = 0.002$) and PR (8.5% *vs* 0.9%; $P = 0.001$) fetal death. No significant difference was found in PR fetal-loss rate before 20 weeks between the first and the second time-cohort ($P = 0.083$).

Technical details

In the second time-cohort, significantly more procedures were completed successfully than in the first time-cohort

(96.8% *vs* 99.0%, $P = 0.001$). The number of attempts per procedure decreased (median, 1 (range, 1–7) *vs* 1 (range, 1–5), $P < 0.001$). From 2001 onward, the fetal liver was the most frequently chosen procedure access site (48.0% in the second cohort *vs* 13.8% in the first cohort, $P < 0.001$). Trends in procedure access sites over time are presented in Figure 1.

Fetal paralysis was applied significantly more frequently (97.8% *vs* 81.3%, $P < 0.001$) and transamniotic needling in a free loop of cord was performed less frequently (3.7% *vs* 33.1%, $P < 0.001$) from 2001 onwards compared with before 2001. No arterial punctures were performed after 2001 (0.0% *vs* 3.2%, $P < 0.001$).

In Table 3, procedures that were followed by severe PR complications (fetal distress resulting in emergency CS or death) are compared with the remaining procedures by univariate analysis. Hydrops was not associated with severe PR complications ($P = 0.315$). *Z*-hemoglobin (number of SDs from median concentration for gestational age), fetal paralysis, procedure access site and unsuccessful IUT were included in a multiple regression model. A positive association with severe PR complications was found for transamniotic ($P = 0.030$) and arterial ($P < 0.001$) transfusion sites, compared with transfusion into the fetal liver. There was a negative association of PR complications with fetal paralysis ($P = 0.034$). Intrahepatic and placental cord insertion sites were equally safe ($P = 0.597$).

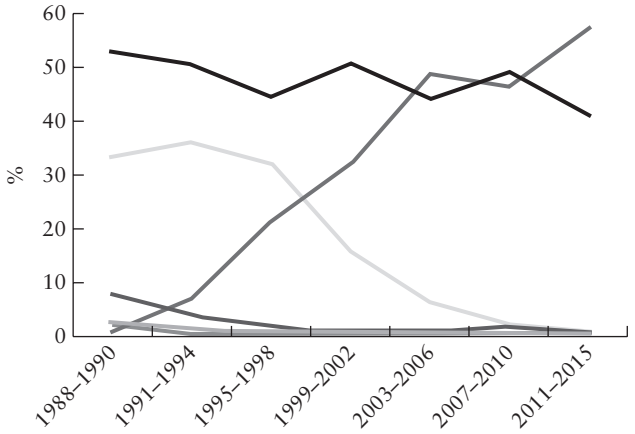

Figure 1 Trends in procedure access sites for intrauterine intravascular blood transfusion between January 1988 and January 2015. ——, liver (plus intraperitoneal); ——, placental cord insertion; ——, transamniotic venous; ——, arterial (cord insertion or transamniotic); ——, intraperitoneal; ——, unknown vessel, heart, chorionic vein.

DISCUSSION

In this cohort of 589 fetuses treated with 1678 IUTs for fetal anemia caused by red-cell immunization, we found an improvement in perinatal survival over time, from 88.6% in 1988–2000 to 97.0% from 2001 onwards. The incidence of PR complications decreased significantly in the last decade. PR loss rates declined from 4.7% to 1.8% per fetus and from 1.6% to 0.6% per procedure, a decrease that approached statistical significance. In spite of our policy not to apply routine antibiotics prior to transfusion, PR infection rate was extremely low (0.1% per procedure). These results suggest that intrauterine treatment for red-cell immunization has become significantly safer in the past decade.

Recently, three other European fetal therapy centers reported on PR complications and loss rates[7,8,17]. Pasman *et al.* found a comparable PR complication rate (1.5%) in 135 procedures performed between 2000 and 2014, although no perinatal death occurred in the 56 fetuses in their study[8]. We found lower overall PR perinatal loss rates compared with another recent European study, by Tiblad *et al.*, in which four of 85 fetuses died as a direct result of the procedure (4.7% per fetus, 1.4% per procedure) performed between 1990 and 2010[7], and with the third study by Sainio *et al.*, which had a 3.8% PR fetal-loss rate[17]. None of these studies compared trends in results over time.

Table 3 Univariate analysis of characteristics of 34 intrauterine intravascular blood transfusions (IUTs) that were followed by severe procedure-related (PR) complications, compared with 1644 remaining procedures in 589 fetuses with anemia caused by red-cell alloimmunization

Characteristic	*IUT with PR complication** (n = *34*)	*Remaining IUTs* (n = *1644*)	*OR (95% CI)*	P
Hydrops at IUT	7 (20.6)	231 (14.1)	1.6 (0.7–3.7)	0.315
GA at IUT (weeks)	31.1 (16.0 to 35.1)	29.9 (16.4 to 37.0)	—	0.411
Z-hemoglobin at IUT†	−7.4 (−12.2 to −3.6)	−6.8 (−11.7 to 1.4)	0.8 (0.7–1.0)	0.016
Fetal paralysis	23 (67.6)	1440 (87.6)	0.2 (0.1–0.5)	0.001
Procedure access site				
Liver	6 (17.6)	546 (33.2)	0.4 (0.2–1.0)	0.065
Placental cord insertion	11 (32.4)	787 (47.9)	0.5 (0.3–1.1)	0.083
Transamniotic ‘free loop’	10 (29.4)	270 (16.4)	2.1 (1.0–4.5)	0.060
Artery	4 (11.8)	20 (1.2)	10.8 (3.5–33.6)	0.001
Intraperitoneal	0 (0)	13 (0.8)	—	1.000
Other‡	3 (8.8)	8 (0.5)	19.8 (5.0–78.2)	0.001
Unsuccessful IUT	3 (8.8)	30 (1.8)	5.2 (1.5–18.0)	0.027

Data are given as *n* (%) or median (range). *Procedures followed by fetal distress resulting in emergency Cesarean section within 24 h or fetal death. †Number of SDs from median concentration for gestational age (GA). ‡Unknown vessel, heart, chorionic vein. OR, odds ratio.

The increase in survival in our study may be explained, in part, by reduced severity of the disease at referral in the second cohort, reflected by a lower hydrops rate and higher hemoglobin concentrations at first IUT[18,19]. This improvement reflects the optimization of the Dutch program for detection and prevention of red-cell antibodies[20,21]. We showed previously that fetal hydrops was associated with adverse outcome, both short- and long-term[18,19], but not with occurrence of PR complications[5], as confirmed in the present study. The decline in number of RhD immunizations during the study period is probably best explained by the introduction of routine prophylactic administration of anti-D in the 30th week of gestation in 1998[22], in addition to postnatal anti-D.

It is likely that the most important factor associated with our low complication rates is the large number of IUTs performed annually at our center (mean, 62 per year *vs* 10, 14 and 38 per year in Tiblad *et al.*[7], Pasman *et al.*[8] and Sainio *et al.*[17], respectively), which enhances operator and team experience and thus also diminishes PR complication rates[6].

We hypothesize that the extensive decline in PR complications is the result of avoiding possibly hazardous techniques in the more recent procedures. Risk factors for adverse outcome were identified previously[5] and were confirmed in the current study as being arterial puncture, transamniotic 'free loop' needling and refraining from fetal paralysis. These technical aspects occurred significantly less frequently in procedures performed from 2001 onwards in our study, compared with procedures carried out before this timepoint. Furthermore, the fetal liver gained impressive popularity as a procedure access site, as this is associated with very low complication and loss rates and is considered to be a safe route of access[5,23,24]. In the previously mentioned studies with higher reported complication rates, 15.5%[7] and 63.8%[17] of transfusions were transamniotic.

Our current study shows that early IUT is still a hazardous procedure, as both NPR and PR complications occur more often before 20 weeks. Early IUT is technically more challenging, resulting in a higher complication risk. Unfortunately, evidence-based studies on the benefit of intravenous immunoglobulin treatment to postpone the first IUT are still lacking. We are currently evaluating the effect of intravenous immunoglobulin in an international multicenter cohort study.

One of the strengths of our study is that all complications were independently and thoroughly classified as PR or NPR. Furthermore, the size of our cohort is considerably larger than those in other published studies.

The retrospective design of this study carries some limitations. For example, the rationale for decisions on technical details of procedures by individual operators is difficult to determine retrospectively. However, because of the available evidence supporting transfusion techniques, randomization into different strategies to identify risk factors prospectively could be considered as unethical[5,8]. Another limitation of this study could be that we did not address neonatal outcomes other than death. This was a deliberate choice, as our focus was on severe PR complications. Furthermore, short- and long-term outcomes of IUTs have recently been thoroughly addressed by our group[19].

Our study demonstrates that IUTs should be a tailored treatment, with the chosen technique fine-tuned to the patient's situation. We advocate that every operator should master all transfusion techniques and maintain experience by performing a sufficient number of transfusions per year in an experienced team. A minimum number of 10 transfusions annually for experienced operators has been suggested[6]. In order to achieve this target, centralization of fetal therapy is necessary.

In summary, we found that IUT for red-cell immunization has become a safer treatment option for fetal anemia. We believe that our current PR fetal-loss rates (1.8% per fetus and 0.6% per procedure) can be considered 'as good as it gets' in experienced hands. For the future, we are focusing our research on non-invasive treatment, such as immunomodulation with intravenous immunoglobulin.

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