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Variations in antenatal management and outcomes in haemolytic disease of the fetus and newborn: an international, retrospective, observational cohort study

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Summary

Background Advances in haemolytic disease of the fetus and newborn have led to numerous treatment options. We report practice variations in the management and outcomes of haemolytic disease of the fetus and newborn in at-risk pregnancies.

Methods In this international, retrospective, observational cohort study, data from cases with moderate or severe haemolytic disease of the fetus and newborn were retrieved from 31 centres in 22 countries. Eligible participants had pregnancies with haemolytic disease of the fetus that led to fetal death at 16+0 weeks or later, those treated antenatally with intrauterine transfusion or intravenous immunoglobulins, or neonates without antenatal treatment who were treated with intensive phototherapy, exchange transfusion, or red blood cell transfusions. All patients had confirmed maternal alloantibodies and an antigen-positive fetus incompatible with the maternal alloantibody. Patients with ABO-incompatibility only were excluded. We assessed serological diagnostics and referrals, antenatal treatment and timing, complications, delivery route, and gestational age at birth. Outcomes were analysed in all eligible participants who had complete data available.

Findings 2443 pregnancies with haemolytic disease of the fetus and newborn treated between Jan 1, 2006, and July 1, 2021, were shared by the centres and analysed between Dec 1, 2021, and March 1, 2023. 23 pregnancies were excluded due to missing information and we included 2420 for further analysis. 1764 (72·9%) of 2420 pregnancies were affected by D-antibodies. 95 (3·9%) of 2420 pregnancies resulted in fetal death. Of the 2325 liveborn neonates, 1349 (58·1%) received any form of antenatal treatment and 976 (41·9%) were only treated postnatally. Median gestational age at referral was 20·4 weeks (IQR 14·9–28·0) and ranged between medians of 10·0 and 26·3 weeks between centres. Severe hydrops at first intrauterine transfusion was present in 185 (14·5%) of 1276 pregnancies, with proportions ranging between 0 and 42% between centres. A median of two intrauterine transfusions (IQR 1–4) were done per pregnancy. The fetal access sites used in intrauterine transfusions varied widely between centres. Non-lethal complications in intrauterine transfusions by transfusion site occurred at a lower rate in intrahepatic approaches (2·0%, 95% CI 1·1–3·3) than in placental insertion (6·9%, 5·8–8·0) and free loop (13·3%, 8·9–18·9). The use and indication for intravenous immunoglobulin administration varied widely. Neonates with intrauterine transfusion were born at a median gestational age of 35·6 weeks (IQR 34·0–36·7), ranging between medians of 33·2 and 37·3 weeks between centres, while neonates without antenatal treatment were born at a median gestational age of 37·3 (IQR 36·3–38·1), ranging between medians of 34·9 and 38·9 weeks between centres.

Interpretation We found considerable variation in antenatal management and outcomes in haemolytic disease of the fetus and newborn between sites in different countries. Our study shows the capacity of the field to gather valuable data on a rare disease and to optimise care.

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Research in context

Evidence before this study

We did not conduct a formal literature search. Preventative efforts in haemolytic disease of the fetus and newborn have drastically decreased its prevalence. Knowledge in this field of maternal-fetal medicine has largely been dependent on single-centre studies with few pregnancies. Considering the many available treatment options (such as intrauterine transfusions, intravenous immunoglobulin, plasmapheresis and induction of delivery), large variations in the management of pregnant patients and fetuses affected might exist between centres.

Added value of this study

This unique international effort, including data from 31 centres in 22 countries, enabled us to reflect on variations in the care of pregnant women with haemolytic disease of the fetus and newborn and outcomes of fetuses at risk of severe fetal anaemia. We found considerable variation in the timing and reason of referral of at-risk pregnancies, presence of hydrops, timing and fetal access sites for intrauterine transfusions, use of treatments to delay the onset of fetal anaemia, and the timing of delivery. These practice variations might result from a paucity of evidence, but could also reflect the availability and applicability of resources in different settings.

Implications of all the available evidence

Approaches in the antenatal management of haemolytic disease of the fetus and newborn vary widely between centres. Through this international collaboration, we established an important basis in maternal-fetal medicine and immunohaematology to deepen our understanding of differences in management. Future studies should focus on consolidating data in an international, prospective registration to identify further opportunities to improve care and unify practices.

Introduction

Haemolytic disease of the fetus and newborn is a pregnancy-related disease in which maternal IgG alloantibodies destroy fetal and neonatal red blood cells, potentially causing severe complications such as fetal anaemia, hydrops fetalis, and death.

Timely identification and monitoring of at-risk pregnancies are crucial to ensure early detection and treatment of fetal anaemia with intrauterine transfusions, to prevent hydrops fetalis and fetal death.[1] Intrauterine transfusions are inherently risky, especially early in pregnancy.[2] In some cases, intravenous immunoglobulins and plasmapheresis can be used to delay the onset of fetal anaemia.[3–8] Induction of preterm delivery is widely accepted in high-risk pregnancies to limit the consequences of increasing IgG transport.[9] However, preterm delivery comes at the expense of fetal maturation and can pose other risks.[10,11]

Anti-D immunoprophylaxis has resulted in a marked decrease in the prevalence of haemolytic disease of the fetus and newborn in high-income countries.[12–14] Research to advance this field of fetal-maternal medicine thereby largely relies on international collaborations between specialised centres that each manage a small number of pregnancies.

Considering the rarity, comparison of practices, and outcomes between centres is essential to optimise care.[15] We aimed to assess current practice in antenatal management and to evaluate clinical outcomes.

Methods

Study design and participants

In this international, retrospective, observational cohort study, the Leiden University Medical Centre initiated the study and invited a total of 46 centres to participate. 30 centres agreed to participate, for a total of 31 (including Leiden University) participating centres from 22 countries. Of the 16 remaining centres, 14 centres did not respond to the invitation or did not have an interest in participating, one centre was unable to achieve judicial and ethical approval within the study timeframe and one centre's participation was put on hold by the Dutch Federation of Medical Universities due to ongoing conflict in Ukraine. Participating centres were from Europe (n=21), North America (n=4), South America (n=3), the Middle East (n=1), Africa (n=1), and Asia (n=1; appendix 1 pp 2–3).

The study was approved by the medical ethical committee of Leiden-Delft-Den Haag (G21.113), adhered to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013; version 2013) and complied with the General Data Protection Regulation. Approval was obtained from institutional review boards or ethical committees of participating centres. Written informed consent was obtained when necessary. The necessity for informed consent forms (ICF) depended on the center. Each center applied for ethical approval independently, with some requiring ICFs and others not.

We gathered all available data from patients with haemolytic disease of the fetus and newborn treated between Jan 1, 2006, and July 1, 2021. Eligible cases had pregnancies that led to fetal death at 16+0 weeks or later; fetuses who were treated antenatally with intrauterine transfusion or intravenous immunoglobulins; or neonates without antenatal treatment who were treated with intensive phototherapy, exchange transfusion, or red blood cell transfusions. All patients had confirmed maternal alloantibodies and an antigen-positive fetus test incompatible with the maternal alloantibody. Patients with only ABO-incompatibility were excluded.

Procedures

Medical records were reviewed, eligibility was determined, and data were entered in an online CastorEDC electronic case report form by investigators between Dec 1, 2021, and March 1, 2023. We collected data on alloantibodies, referral, antenatal and postnatal management, and outcomes. The electronic case report form contained built-in validations. Remaining inconsistencies were checked with local investigators. We refer to the supplementary statistical analysis plan for further specifications. The study adhered to the STROBE reporting guideline. This manuscript covers antenatal management. Postnatal outcomes will be reported in a separate manuscript elsewhere.

We defined four antenatal referral categories: referral for maternal alloimmunisation based on serological diagnostics without suspected fetal anaemia, referral for maternal alloimmunisation with suspected fetal anaemia based on the peak systolic velocity of the middle cerebral artery,[16,17] referral for signs of fetal hydrops (distinct rim of ascites, abundant ascites, skin oedema, pericardial effusion, or pleural effusion), and referral for obstetrical care not related to haemolytic disease of the fetus and newborn.

Mild hydrops was defined by a distinct rim of ascites, without skin oedema, pericardial effusion, or pleural effusion.[18] Severe hydrops was defined by abundant ascites, skin oedema, pericardial effusion, or pleural effusion.

We categorised complications arising from intrauterine transfusions into two groups: fetal death within 24 h after intrauterine transfusion and non-lethal complications. Non-lethal complications included bleeding from puncture site, cord occlusion, fetal heart rate abnormalities, needle dislocation, procedure failure, intrauterine infection, preterm prelabour rupture of membranes, and preterm emergency delivery. To quantify differences in complications by fetal access site, we describe the rate of fetal death and non-lethal complications in intrauterine transfusions separately for intrahepatic vein, placental cord insertion, free loop, a combination of intrahepatic and intraperitoneal, and intraperitoneal access only (figure 1). We also did a sub-analysis for emergency caesarean section.

Statistical analysis

We finalised a statistical analysis plan before analysis (appendix 2).[19] However, during the review process, some aspects of the statistical analysis plan were reconsidered, resulting in a more descriptive approach to the presentation of the findings.

Outcomes were analysed in all eligible participants who had complete data available.

Continuous data is presented as median (IQR) and categorical data as proportions. Statistical analyses were done using SPSS Statistics (version 28.0). Clopper-Pearson CIs were used to accompany proportions by binomial 95% CIs. The proportion of complications was also reported by gestational age at procedure. In the analysis for emergency caesarean section, only intrauterine transfusions done at or after 24 weeks' gestation were included, excluding intrauterine transfusions that led to intrauterine fetal death. To prevent confounding on gestational age at birth we excluded neonates delivered due to intrauterine transfusion complications from that descriptive analysis. Numerators and denominators were reported to address missing data. For privacy and confidentiality, we report centre names pseudonymously.

Role of the funding source

There was no funding source for this study.

Results

Data on 2443 pregnancies with haemolytic disease of the fetus and newborn that occurred between Jan 1, 2006, and July 1, 2021, were shared by the centres (appendix 1 pp 2–3). 23 pregnancies were excluded due to missing information and we included 2420 for further analysis. Of these, 95 pregnancies (3·9%) resulted in perinatal death, 1349 (55·7%) resulted in neonates who received antenatal treatment, and 976 (40·3%) resulted in neonates who received postnatal treatment only (table 1). 1764 (72·9%) of 2420 pregnancies were affected by D-antibodies (appendix 1 pp 4–13, 22–23).

The reason for referral was known in 2174 (89·8%) of 2420 pregnancies. Those pregnancies with known reasons were referred at a median gestational age of 20·4 weeks (IQR 14·9–28·0), ranging between medians of 10·0 and 26·3 weeks between centres (figure 2A). Early referral for maternal alloimmunisation based on serology without suspected fetal anaemia concerned 1825 (83·9%) of 2174 pregnancies at a median gestational age of 19·0 weeks (IQR 13·9–26·7). 977 (53·5%) of these 1825 fetuses subsequently received treatment with one or more intrauterine transfusions. At the time of the first intrauterine transfusion, 63 (6·4%) of 977 fetuses presented with mild hydrops and 87 (8·8%) with severe hydrops.

314 (14·4%) of 2174 pregnancies were referred for suspected fetal anaemia on ultrasound (based on the peak systolic velocity of the middle cerebral artery or the presence of fetal hydrops) at a later median gestational age of 27·6 weeks (22·6–31·1). Among these, 288 (91·7%) of 314 pregnancies subsequently received treatment with one or more intrauterine transfusions. At the time of the first intrauterine transfusion, mild hydrops was present in 27 cases (8·6%) and severe hydrops in 78 cases (24·8%). The proportion of pregnancies referred for suspected fetal anaemia on ultrasound ranged between 0% and 50% between centres (figure 2B). Centre-specific screening and monitoring characteristics are included in appendix 1 (pp 14–16).

35 (1·6%) of 2174 pregnancies were referred for obstetrical care not related to haemolytic disease of the fetus and newborn at a median gestational age of 20·1 weeks (IQR 12·3–26·3). In these patients,

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See **Online** for appendix 1 and 2

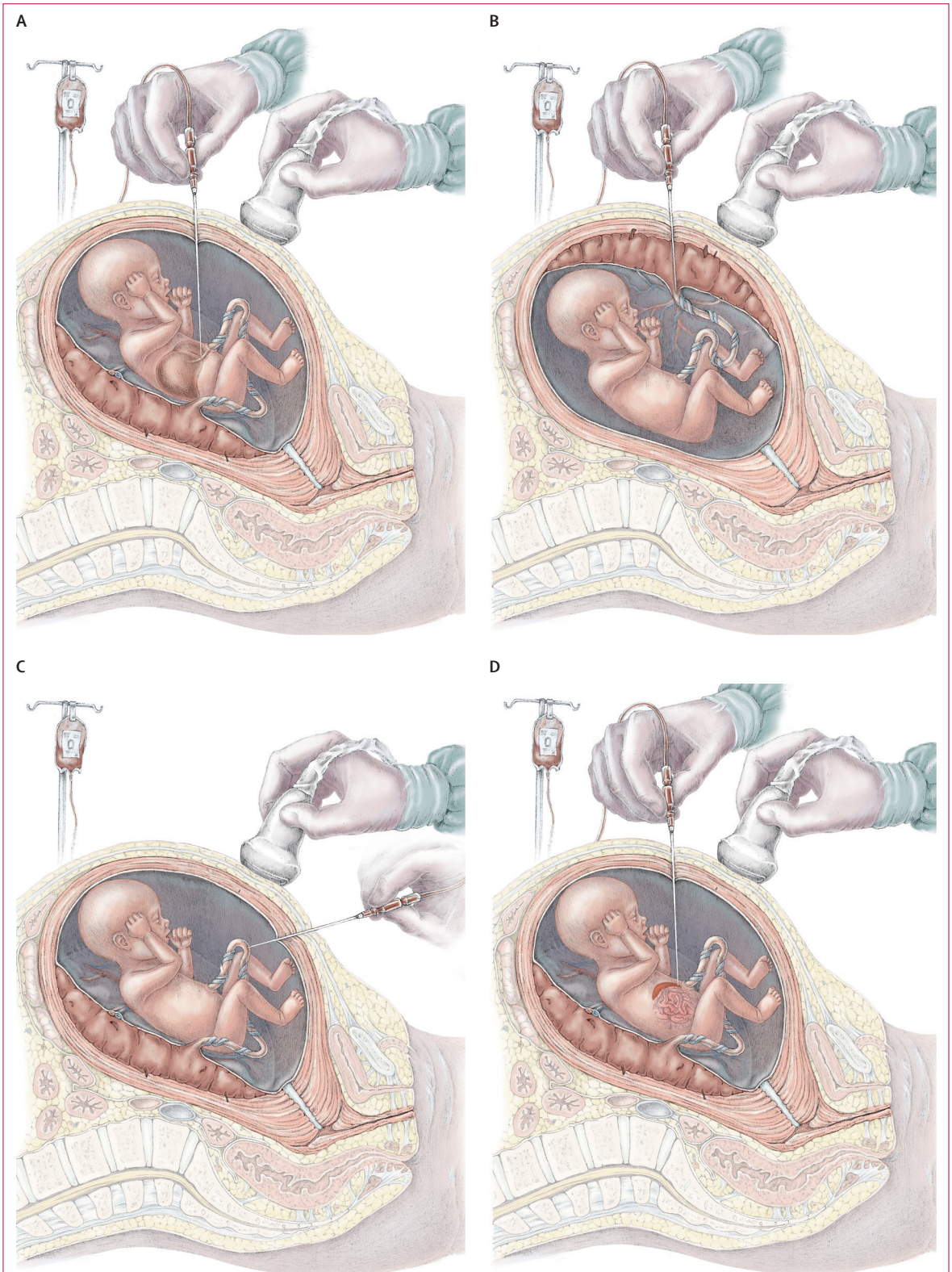

Figure 1: **Fetal access sites in intrauterine transfusions**
(A) Intrahepatic approach in the intrahepatic vein. (B) Placental insertion of the umbilical cord. (C) Transamniotic puncture of the umbilical cord (free loop). (D) Intraperitoneal transfusion into the peritoneal space. Scientific illustration by Amanda Gautier.

alloimmunisation was diagnosed after initial referral. 17 (48·6%) received treatment with one or more intrauterine transfusions. At the time of the first intrauterine transfusion, mild hydrops was present in zero patients and severe hydrops was present in three (17·6%) of 17 pregnancies.

Information on the gestational age at referral and the presence of hydrops at first intrauterine transfusion was available in 1276 (90·0%) of 1418 pregnancies with at least one intrauterine transfusion or haemolytic disease of the fetus and newborn-related fetal death. Among these, severe hydrops was reported in 185 (14·5%) of 1276 pregnancies (referred at a median gestational age of 22·3 weeks [IQR 18·0–27·4] with 3 days [IQR 1–53] between referral and first intrauterine transfusion). Mild hydrops was reported in 90 (7·1%) of 1276 pregnancies (referred at a median gestational age of 20·7 weeks [15·5–25·5] with 16 days [1–73] between referral and first intrauterine transfusion). Hydrops was absent in 1001 (78·4%) of 1276 pregnancies (referred at a median gestational age of 20·1 weeks [15·0–28·0] with 34 days [4–80] between referral and first intrauterine transfusion). The proportion of severe hydrops at first intrauterine transfusion ranged between 0% and 43% across centres (figure 2C).

A total of 4016 intrauterine transfusions were done with a median of two (IQR 1–4) intrauterine transfusions per pregnancy, ranging between a median of two and six intrauterine transfusions per pregnancy between centres (appendix 1 pp 17–19). Median gestational age at first intrauterine transfusion was 28·0 weeks (IQR 23·9–31·1), ranging between a median of 24·1 and 30·0 weeks across centres. In 3753 (93·5%) of 4016 intrauterine transfusions with data on the used approach, placental insertion was most commonly used (2262 [60·3%]), followed by intrahepatic transfusion (776 [20·7%]), free loop (280 [7·5%]), a combination of intrahepatic and intraperitoneal transfusion (251 [6·7%]), and intraperitoneal transfusion only (134 [3·6%]). Intracardiac intrauterine transfusions were less frequent (22 [0·6%]). The proportion of intrauterine transfusions performed at the placental insertion ranged between 18 (13%) of 141 performed at centre 6 and 96 (97%) of 99 performed at centre 18 (figure 3A).

Data on complications was available in 3613 (90·0%) of 4016 intrauterine transfusions. Complications occurred in 250 (6·9%) of 3613 transfusions and most frequently encompassed bleeding from puncture site (102 [2·8%] of 3613), emergency caesarean section less than 24 h after procedure (40 [1·1%]), fetal death less than 24 h after procedure (30 [0·8%]), procedure failure (21 [0·6%]), needle dislocation (15 [0·4%]) and fetal heart rate abnormalities (13 [0·4%]). Maternal complications occurred in 11 (0·3%) of 3613 intrauterine transfusions. Specific details of maternal complications are reported in appendix 1 (p 21).

	Liveborn, with any form of antenatal treatment (n=1349)	Liveborn, without antenatal treatment (n=976)
Sex of the fetus		
Female	583 (48·7%)*	405 (41·5%)
Male	614 (51·3%)*	571 (58·5%)
Primary alloantibody		
Anti-D	1019 (75·5%)	734 (75·2%)
Anti-K1	188 (13·9%)	34 (3·5%)
Others	142 (10·5%)	208 (21·3%)
Gravidity	3 (2–4)	3 (2–4)
Parity	2 (1–3)	1 (1–2)
Gestational age at referral (weeks)	21·0 (15·3–28·0)†	20·4 (14·1–28·7)‡
Obstetrical care, not haemolytic disease of the foetus and newborn-related	12 (0·9%)	18 (1·8%)
Maternal alloimmunisation, no suspected fetal anaemia	937 (69·5%)	822 (84·2%)
Suspected fetal anaemia	215 (15·9%)	19 (1·9%)
Signs of hydrops fetalis and suspected fetal anaemia	57 (4·2%)	5 (0·5%)
Unknown	128 (9·5%)	34 (3·5%)
Antenatal treatment	1349 (100%)	NA
Intrauterine transfusion only	1259 (93·3%)	NA
Intravenous immunoglobulin only	11 (0·8%)	NA
Intrauterine transfusion + intravenous immunoglobulin	60 (4·4%)	NA
Intravenous immunoglobulin + plasmapheresis	2 (0·1%)	NA
Intrauterine transfusion + intravenous immunoglobulin + plasmapheresis	17 (1·3%)	NA
Number of intrauterine transfusions	2 (1–4)	NA
Gestational age at first intrauterine transfusion	28·3 (24·3–31·3)	NA
Gestational age at last intrauterine transfusion	32·7 (31·3–34·0)	NA
Caesarean section	821 (60·9%)	416 (42·6%)
Gestational age at birth (weeks)§	35·6 (34·0–36·7)	37·3 (36·3–38·1)
Birthweight (g)	2640 (2270–2980)	2980 (2610–3310)
Haemoglobin level at birth (g/dL)¶	12·4 (10·4–14·3)	14·2 (11·7–16·3)

Data are n (%) or median (IQR). Race and ethnicity data were not collected. NA=not applicable. *In 1197 (88·7%) neonates in whom the sex was known. Sex was known in all liveborn neonates without antenatal treatment.†In 1205 (89·3%) pregnancies in which the gestational age at referral was known. Referral data was unavailable in 112 (8·3%) pregnancies from a single centre. ‡Gestational age at referral was unavailable in 152 (15·6%) pregnancies with liveborn neonates without antenatal treatment. §In 898 (92·0%) of antenatally referred liveborn cases managed without antenatal treatment. ¶In 1017 (75·4%) neonates with antenatal treatment and 838 (85·9%) neonates without antenatal treatment.

Table 1: **Baseline clinical characteristics of liveborn cases**

Data on complications and fetal access site used in intrauterine transfusions were available in 3465 (86·3%) of 4016 procedures. Fetal death within 24 h after the procedure occurred in 29 (0·8%) of 3465 intrauterine transfusions. The proportion of fetal death was 1·2% (95% CI 0·2–3·5) in intrahepatic and intraperitoneal transfusion, 0·8% (0·4–1·2) in placental insertion, 0·8% (0·0–4·2) in intraperitoneal transfusion, 0·5% (0·0–2·8) in free loop, 0·6% (0·2–1·5) in intrahepatic approaches, and 15·8% (3·4–39·6) in intrauterine

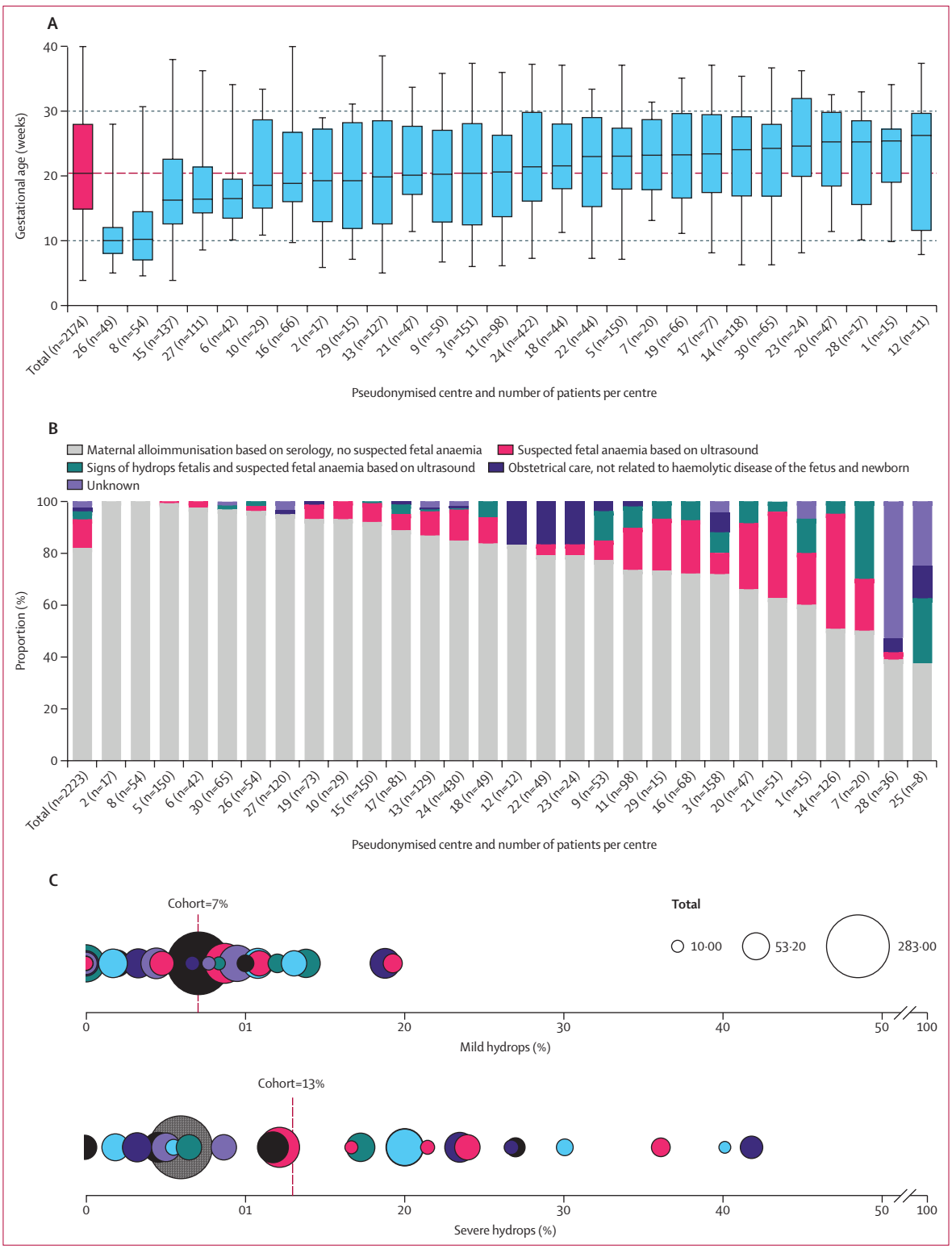

Figure 2: **Timing of referral and fetal condition at first intrauterine transfusion**
(A) Gestational age at referral for the included cohort by centre. Boxplots represent the median and IQR and the error bars represent range. (B) Distribution of reasons for referral by centre. Pseudonymised centres and centre-specific totals are depicted on the x-axis. (C) Distribution of the proportion of mild and severe hydrops fetalis at the first intrauterine transfusion by centre. Each bubble represents a centre. The size of the bubble represents the number of cases.

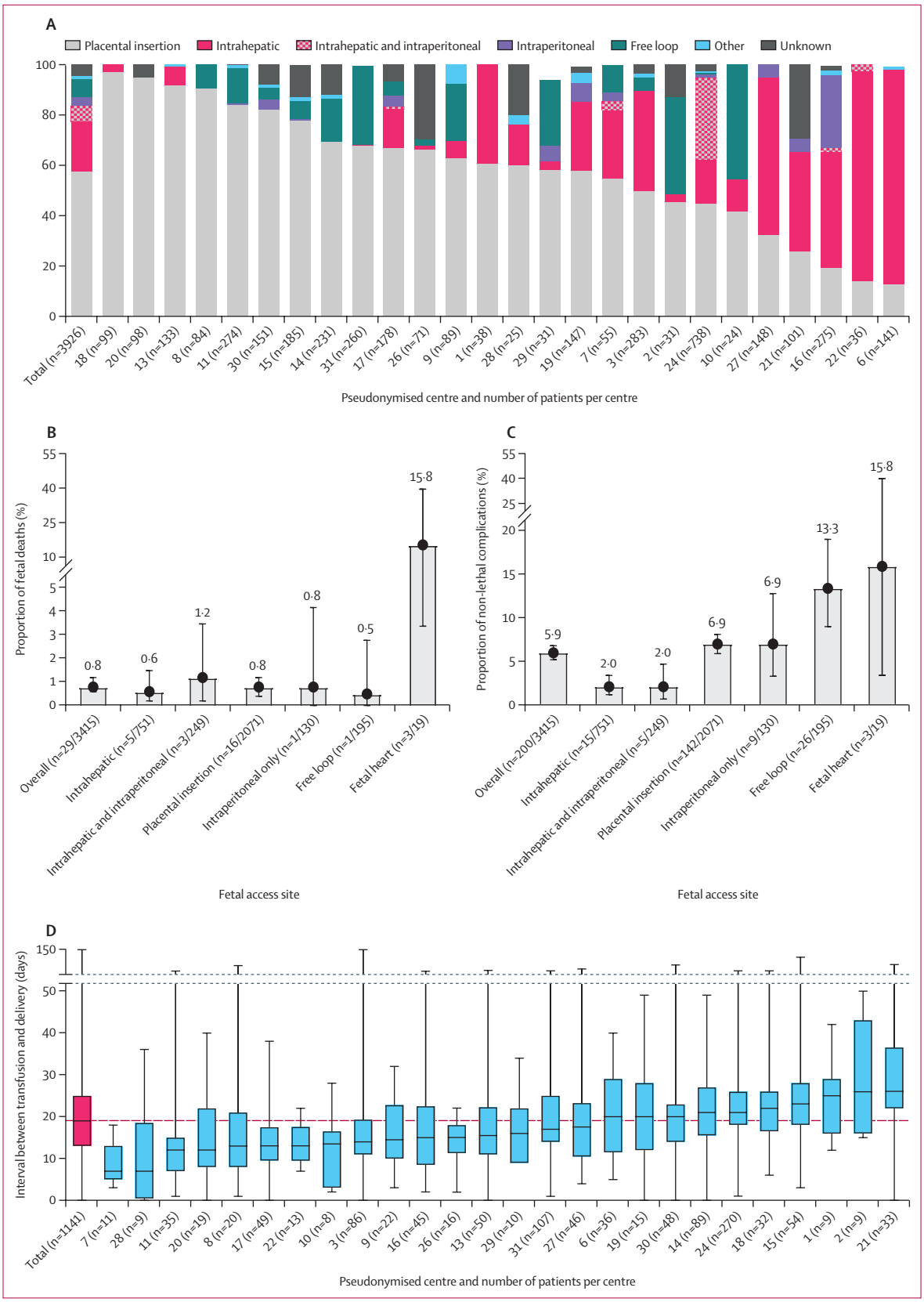

***Figure 3*: Intrauterine transfusion fetal access sites, complications, and interval between the last intrauterine transfusion and delivery by centre**

(A) Fetal access sites used in intrauterine transfusions by centre. (B) Complications resulting in fetal death by fetal access site. Error bars indicate 95% CI. (C) Non-lethal complications by fetal access site. Error bars indicate 95% CI. (D) Distribution of the interval between the last intrauterine transfusion and delivery by centre. Error bars indicate range

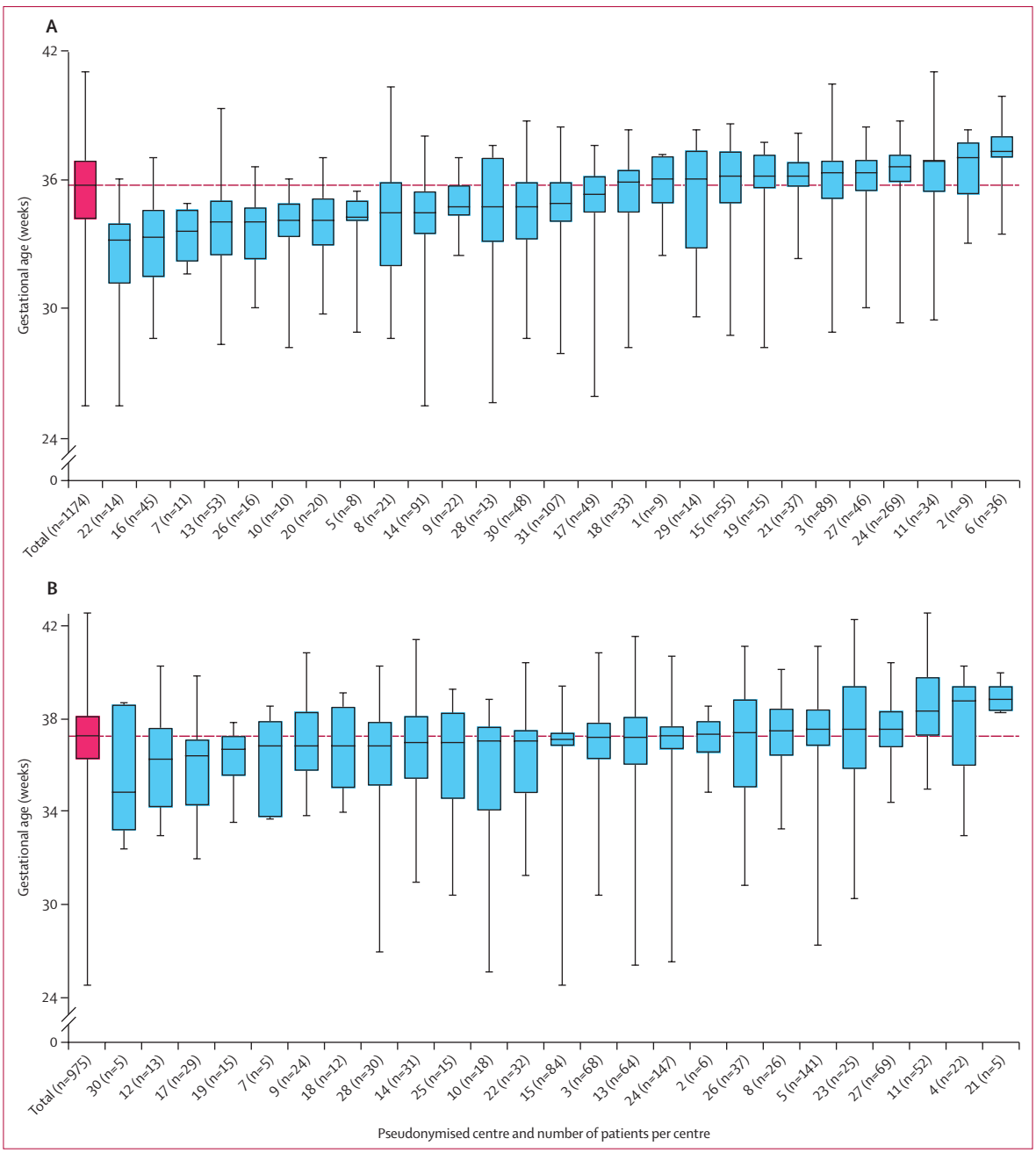

Figure 4: **Gestational age at birth by centre**
(A) Median gestational age at birth for neonates treated with at least one intrauterine transfusion by centre. (B) Median gestational age at birth in neonates without antenatal treatment by centre. Error bars indicate range.

transfusions in the fetal heart (figure 3B). From a gestational age of 23+0 onwards we saw decreasing rates of fetal death in intrauterine transfusions (appendix 1 p 20). No fetal deaths occurred in 908 intrauterine transfusions done after 32+0 weeks.

The proportion of non-lethal complications was 13·3% (95% CI 8·9–18·9) in free loop, 6·9% (3·2–12·7) in intraperitoneal, 6·9% (5·8–8·0) in placental insertion, 2·0% (1·1–3·3) in intrahepatic, 2·0% (0·6–4·6) in intrahepatic and intraperitoneal approach, and 15·8% (3·3–39·6) in intrauterine transfusions in the fetal heart (figure 3C). We found no difference in the proportion of non-lethal complications per gestational age at which the procedure was done (appendix 1 p 20).

The proportion of emergency caesarean section after intrauterine transfusion performed at or after 24+0 weeks gestation was 1·5% (95% CI 0·3–4·5, three of 194 patients) in free loop, 1·5% (1·0–2·1, 30 of 2055 patients) in

placental insertion, 0·5% (0·1–1·4, four of 746 patients) in intrahepatic transfusion, and 0·4% (0·0–2·2, one of 246 patients) in intrahepatic and intraperitoneal transfusion. Emergency caesarean section was not required in 129 intraperitoneal intrauterine transfusions.

Antenatal treatment was provided by 28 of 31 centres, including 1428 pregnancies, of which 101 (7%) received intravenous immunoglobulins, plasmapheresis, or a combination of the two to delay the onset of fetal anaemia. Among these 101 pregnancies, 68 (5%) received intravenous immunoglobulins and intrauterine transfusion, 20 (1%) received intravenous immunoglobulins, plasmapheresis and intrauterine transfusion, 11 (1%) received only intravenous immunoglobulins and two (<1%) received only intravenous immunoglobulins and plasmapheresis. Of the 28 centres that provided antenatal treatment, 16 used treatment options to delay the onset of fetal anaemia. 12 centres provided intravenous immunoglobulins early in pregnancy, ranging between 2% and 27% of pregnancies by centre. Intravenous immunoglobulins were started at a median gestational age of 15·0 weeks (IQR 12·8–16·6) and a median of 8 doses (IQR 5–11) were administered. Among 79 pregnancies treated with intravenous immunoglobulins, 54 (68·%) had no previous history of perinatal death or need for intrauterine transfusion. 68 (86·%) of 79 pregnancies required intrauterine transfusion, with the first intrauterine transfusion at a median gestational age of 21·1 weeks (IQR 17·9–24·8) and a median of four intrauterine transfusions (IQR 2–5) per pregnancy. Five centres provided intravenous immunoglobulins combined with plasmapheresis, ranging between 1% and 22% of pregnancies by centre. Treatment was started at a median of 17·0 weeks (IQR 15·6–20·8) with a median of three plasmapheresis treatments (IQR 3·0–3·5) per pregnancy. Among 22 pregnancies in which this combination (intravenous immunoglobulins and plasmapheresis) was given, eight (36·4%) had no previous pregnancy complicated by demise or need for intrauterine transfusion, but 20 (90·9%) required intrauterine transfusion in this pregnancy, with the first intrauterine transfusion at 19·8 weeks (IQR 21·4–26·0) and a median of three intrauterine transfusions (IQR 2–5) per pregnancy.

Fetal death occurred in 95 (3·9%) of 2420 pregnancies, at a median of 22·4 weeks (IQR 20·1–28·9). Cause of death was known in 78 cases, of which 64 were directly due to haemolytic disease of the fetus and newborn. Fetal death occurred in 64 (4·8%) of 1336 of all pregnancies in which an intrauterine transfusion was done for fetal anaemia. Characteristics of these 64 pregnancies are displayed in appendix 1 (pp 22–23). In 41 (64%) of 64 pregnancies, demise was related to severe fetal anaemia or severe hydrops. In 52 (81·%) of 64 pregnancies, fetal death occurred after intrauterine transfusion at a median gestational age of 22·3 weeks (IQR 19·7–26·5). Among these, procedure-related demise within 24 h after intrauterine transfusion occurred in 30 (58%) of 52 pregnancies. Another 22 pregnancies (42%) resulted in fetal death more than 24 h after an intrauterine transfusion because of severe hydrops or severe fetal anaemia (19 [86%] of 22), fetal infection (one [5%]), intrauterine intraventricular haemorrhage (one [5%]), or acute chorioamnionitis (one [5%]). Five (8%) of 64 pregnancies were terminated: three because of persistent severe hydrops and poor prognosis, one due to a fear of complications, and one due to maternal-mirror-syndrome.

Gestational age at birth was known in 1174 (91·6%) of 1282 neonates treated with intrauterine transfusion who were not delivered owing to procedure-related complications. The median gestational age at birth was 35·7 weeks (IQR 34·1–36·9), ranging between medians of 33·2 and 37·3 weeks between centres (figure 4A). This range between centres is also reflected in the median gestational age at last intrauterine transfusion, which was 32·6 weeks (IQR 31·3–33·9), ranging between 30·7 and 34·9 weeks between centres (appendix 1 p 24). Also, the time between last intrauterine transfusion and birth was 19 days (IQR 13·0–25·0), ranging between medians of 7 and 26 days between centres (figure 3D). 753 (59·2%) of 1268 neonates treated with intrauterine transfusion were delivered through caesarean section, ranging between 28% and 100% between centres.

In 975 (99·9%) of 976 neonates who did not receive antenatal treatment, the gestational age at birth was 37·3 weeks (IQR 36·3–38·1), ranging between medians of 34·9 and 38·9 weeks between centres (figure 4B). Of 976 neonates who did not receive antenatal treatment, 420 (43·4%) were delivered through caesarean section, ranging between 17% and 100% between centres (appendix 1 p 25).

Discussion

This unique international effort, including data from 31 centres in 22 countries, enabled us to reflect on variations in the care of pregnant women with haemolytic disease of the fetus and newborn and outcomes of fetuses at risk of severe fetal anaemia. We found considerable variation in the timing of referral of at-risk pregnancies, presence of hydrops, timing of intrauterine transfusions, fetal access sites, use of treatments to delay the onset of fetal anaemia, and the timing of delivery. These practice variations might result from a paucity of evidence, but could also reflect the availability and applicability of resources.

We observed a wide variation in referral strategies. Some centres primarily receive pregnancies immediately after serological identification of alloimmunisation, whereas others receive pregnancies with suspected fetal anaemia based on ultrasound. These variations might be explained by differences in screening and monitoring guidelines to identify at-risk pregnancies, substantiated by the range in gestational age at referral. Importantly, we found that the gestational age at referral

in pregnancies with severe hydrops at first intrauterine transfusion was higher than in those without hydrops. It is imperative to identify, monitor, and treat high-risk pregnancies to prevent severe hydrops, which has been shown to be associated with adverse neurodevelopmental outcome.[20]

All centres with antenatally-treated pregnancies performed intrauterine transfusions. Of these centres, 60% administered intravenous immunoglobulins and 20% provided combined plasmapheresis and intravenous immunoglobulins. These treatments have been described to delay the onset of fetal anaemia with a history of early onset haemolytic disease of the fetus and newborn.[3,5,6,21] We found that the application of intravenous immunoglobulins has been broader than previously documented in the literature, as most pregnancies treated with intravenous immunoglobulins did not have a previous history of early onset haemolytic disease of the fetus and newborn. These findings could reflect an absence of consensus on the application of these treatments, but also might be explained by a paucity of resources for intrauterine transfusions, or challenges in performing intrauterine transfusions.

We found an overall preference for performing intrauterine transfusions through the placental insertion or intrahepatically. Considering the equal distribution of anterior and posterior placentas, the extent of the range in both approaches is suggestive that some centres might choose to perform a transplacental transfusion, whereas others might not.[22] The access site used might largely depend on previous training and personal preferences. Given the rarity of intrauterine transfusions, determining complication rates by access site is challenging. This study has enabled us to approach this.

We found no clinically relevant differences in fetal death rate or emergency caesarean section between fetal access sites, however, we report that the rate of non-lethal complications was lower in intrahepatic approaches than in placental insertion and free loop. Although we could correct for gestational age at the procedure and presence of severe hydrops, we could not determine the effect of other potential confounders such as placental position, maternal age, maternal BMI, use of fetal paralysis,[2] or clinicians' experience. Despite these limitations, we conclude that intrahepatic transfusions had a lower rate of non-lethal complications than in placental insertion and free loop.

Fetal death rate due to intrauterine transfusions was highest in earlier gestational age, similar to previous studies.[2,23] We found no fetal deaths as a complication of intrauterine transfusions performed at 32+0 weeks or later, which further supports the finding that fetal death is increasingly rare with increasing gestational age.

As this study was carried out by a large variety of centres with varying numbers of intrauterine transfusions performed and considering the exposure required to maintain competence in intrauterine transfusions,[24] it is likely that the contribution of centres that did more intrauterine transfusions weighted down the rate of fetal demise. We did not aim to assess the performance of centres specifically, and thus did not request data on the number of intrauterine transfusions performed yearly. Previous single-centre studies have reported varying survival rates after intrauterine transfusion ranging from 88·9% to 100%,[4] underlining the hypothesis that fetal demise rates are centre-specific and depend on several factors, including the timing of referral and the clinicians' experience.

Lastly, we found a 4-week variation between centres in gestational age at birth. This might be explained by differences in specialists' perspectives or guidelines regarding the timing of the last intrauterine transfusion and delivery, considering the range of gestational age at that procedure and at birth. This analysis, however, might be confounded as we were unable to correct for other reasons for delivery. Nevertheless, we conclude that over two thirds of neonates were born preterm, with a potentially higher risk of long-lasting medical disabilities compared with full term gestation.[10] Considering the risks of preterm delivery and the low risk of fetal death in intrauterine transfusions after 32+0 weeks, we believe that the field should explore the potential of delivery past 37+0 weeks.

Approximately half of neonates were delivered through caesarean section, exceeding the global average of 21·1%.[25] In some centres most neonates were born by caesarean section, which might again highlight differences in guidelines.

The retrospective study design and its inherent reliance on available and generally heterogeneous data, imposes limitations on the interpretation. However, through joint collection we were able to gather unique data providing original insights across many centres in a rare disease. Included centres were mostly in high-income countries. Despite efforts to include centres across various global regions, we encountered a dearth of information on availability of antenatal identification and management of haemolytic disease of the fetus and newborn. In this process, we discovered global inequalities in the availability of resources for haemolytic disease of the fetus and newborn.[26]

To conclude, we found remarkably different approaches in the antenatal management of haemolytic disease of the fetus and newborn across centres, highlighting the paucity of consensus. We aim to consolidate experience and knowledge in an international, prospective registration to accelerate research in this rare disease and to identify further opportunities to improve care. These endeavours will aid the field to unify current and future practices.[27,28]

Contributors

DPdW, EL, and EJTV were chief investigators and responsible for project administration. DPdW, EL, MdH, JGvdB, and EJTV conceptualised, designed and supervised the study and developed the statistical analysis

plan. DPdW, EJTV, and EL accessed and verified the data. DPdW and EJTV drafted the first manuscript and performed statistical analyses. All authors were responsible for data acquisition, investigation and critically revised the manuscript for important intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DPdW is doing a PhD programme partly funded by Momenta Pharmaceuticals, which was acquired by Johnson & Johnson, and is an investigator for a phase 2 trial (NCT03842189) of a new drug for the treatment of haemolytic disease of the fetus and newborn. EL is a sub-investigator for a phase 2 trial (NCT03842189) of a new drug for the treatment of haemolytic disease of the fetus and newborn, which is sponsored by Janssen Pharmaceuticals. RD reports paid lectures and participation in studies for Janssen Pharmaceuticals. PM received payment for a lecture from CSL Behrin. PM and J-MJ reports participation in an advisory board for haemolytic disease of the fetus and newborn of Janssen Pharmaceuticals in December, 2023, and both report participation in a phase 3 trial (NCT05912517) of a new drug for the treatment of haemolytic disease of the fetus and newborn, which is sponsored by Janssen Pharmaceuticals. ET is the principal investigator for Janssen-sponsored trials Unity and Clarity in Sweden and an advisory Board Member and Steering Committee member for Janssen Pharmaceutical on haemolytic disease of the fetus and newborn and FNAIT programmes. TPS is a member of the board of the International Society of The Fetus as a Patient and member of the expert committee for Gynaecology and Obstetrics at Ministry of Health, Republic of Slovenia. EJTV is the principal investigator for a phase 2 trial (NCT03842189) and phase 3 trial (NCT05912517) of a new drug for the treatment of haemolytic disease of the fetus and newborn, which is sponsored by Janssen Pharmaceuticals. All other authors report no competing interests or financial disclosures.

Data sharing

The data that support this study cannot be shared openly due to reasons of sensitivity and to protect the participants privacy. Data are located in a controlled access data storage at Leiden University Medical Centre.

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