Review

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The Recurrence Risk of Fetomaternal Hemorrhage

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Abstract
Massive fetomaternal hemorrhage (FMH) can cause devastating pregnancy outcomes. Perinatal prognosis may be improved by intrauterine transfusion, but the appropriate management for these pregnancies remains unclear. To determine the recurrence risk of FMH after intrauterine transfusion, we performed a systematic review of all case reports/series of patients with proven FMH treated with intrauterine transfusion and who had subsequent follow-up of at least 72 h until delivery. This revealed 13 cases, with 1 additional case from our institution. Ten patients (71.4%) had a second episode of FMH requiring a second intrauterine transfusion. Five patients (35.7%) required at least 3 intrauterine transfusions. The time interval between intrauterine transfusions was progressively reduced. The gestational age at the onset of signs/symptoms was 26.6 ± 2.1 weeks, and gestational age at delivery was 34.2 ± 4.2 weeks. Two cases of fetal demise (14.3%) and no neonatal deaths were recorded. Limited postnatal follow-up on 8 neonates was normal. The mean neonatal hemoglobin and transfusion rates were 13.2 ± 5.7 g/dL and 33.3%, respectively. Close fetal monitoring, likely daily, is necessary to recognize FMH recurrence. Several transfusions may be necessary once FMH is diagnosed if pregnancy is allowed to continue >72 h.

Background

Fetomaternal hemorrhage (FMH) is defined by the transfer of fetal blood into the maternal circulation during pregnancy. It occurs in the majority of pregnancies, usually without any maternal or fetal risk factors or consequences [1]. There is no standard definition for FMH, and the incidence varies depending on the fetal blood volume that is considered significant. If all degrees of FMH are included, the incidence increases during pregnancy: 4% in the first trimester, 12% in the second trimester, 45%

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in the third trimester, and 60% during delivery [1, 2]. Massive FMH is defined at 30 or 80 mL with an incidence of 0.3 or 0.1%, respectively [3].

Pathophysiologically, FMH disrupts the fetomaternal circulatory interface and trophoblast damage due to inflammatory and mechanical factors, although understanding the etiology remains incomplete [4]. It has been known that FMH can result from invasive obstetrical procedures (e.g., amniocentesis), trauma, placental abruption, and labor augmentation with oxytocin, among others [3, 5]. Case reports have described a possible association of FMH with other pregnancy and intrapartum events like preeclampsia [6] or the placement of intrauterine pressure catheter [7]. Massive FMH may recur in a subsequent pregnancy [8, 9].

Massive FMH often leads to adverse pregnancy outcomes, including stillbirth, hypoxic-ischemic encephalopathy, prematurity, and severe neonatal anemia [3]. Nearly half of the cases of massive FMH are only diagnosed in the early neonatal period or present as fetal death, but precise estimates of adverse outcomes are unknown [10].

Early detection of FMH is critical [10]. Clinical examination, nonstress test (NST), and routine ultrasonography are often ineffective. Decreased fetal movement is nonspecific for fetal anemia [11]. NST can show nonspecific patterns of decelerations. Sinusoidal pattern clearly indicates that fetal anemia must be suspected and managed [12, 13]. Middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurement may have a role in the evaluation and monitoring of suspected fetal anemia [14–16]. The detection of fetal cells in the maternal blood is necessary for the confirmation of FMH. The most widely used test remains the Kleihauer-Betke test; another methods are flow cytometry and liquid chromatography [12].

The management of massive FMH mainly depends on the gestational age of diagnosis, availability of cordocentesis that allows for fetal blood sampling to diagnose fetal anemia and perform fetal transfusion if needed, and the capability of the neonatal intensive care unit (NICU). When the fetus is at 32–34 weeks and in the presence of fetal compromise, delivery may be justified. Before 32 weeks of gestation, correction of the anemia in utero should be considered. After 32 weeks, the risk of complications of intrauterine transfusion (IUT) should be balanced with the risk of prematurity and/or neonatal transfusion [16]. When FMH occurs before 32 weeks, IUT is a well-established procedure to treat fetal anemia [17], but it is still unclear what is the proper monitoring of these pregnancies after the first IUT and what is the recurrence rate. The objective of our study was to determine the recurrence rate of FMH after IUT in order to understand the natural history of FMH and therefore improve fetal outcomes.

Data Sources

This review was performed according to a protocol designed a priori and recommended for systematic review and meta-analysis [18]. Electronic databases (i.e., MEDLINE, Scopus, OVID, Web of Science) were searched from their inception until December 2017. Search terms used were a combination of keywords: "fetomaternal hemorrhage," "massive fetomaternal hemorrhage," "severe fetomaternal hemorrhage," "fetomaternal transfusion," "intrauterine transfusion," "in utero transfusion," "in utero treatment," "fetal anemia," "non-immune hydrops fetalis." No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and eligibility of the studies were independently assessed and reviewed by two authors (L.T., V.B.). Differences were discussed, and consensus was reached.

We included all case reports and case series of proven FMH in singleton gestation treated with IUT with subsequent delay until delivery of at least 72 h. Proven FMH was defined as a pregnancy with a positive laboratory test (Kleihauer-Betke test or liquid chromatography method) and a diagnosis of fetal anemia and lack of other etiologies for fetal anemia. Fetal anemia was defined as a hemoglobin of <10 g/dL and/or hematocrit of <30% on cordocentesis [19]. One additional case at our institution was included. The Institutional Review Board approval was obtained, and the patient provided documented informed consent.

Exclusion criteria included: FMH diagnosed after delivery or during pregnancy that did not require IUT, massive FMH followed by immediate delivery, FMH treated with 1 course of IUT and subsequent delivery within 72 h, and FMH not confirmed by laboratory tests. Cases in which delivery occurred within 72 h of the first IUT for FMH were excluded in an effort to allow sufficient time to establish a natural history of recurrence.

Fetuses receiving IUT for severe fetal anemia associated with other causes, such as red cell alloimmunization, congenital infection, congenital anomalies and genetic disorders were excluded. Multiple gestations were excluded. Maternal and neonatal characteristics were extracted. Details of the IUT were also obtained. Histopathological examination of placenta was reviewed.

The primary outcome was the recurrence rate of FMH after IUT. Secondary outcomes were: latency period from FMH onset to birth, time interval between IUTs, total amount of blood volume transfused before birth, gestational age at birth, mode of delivery, incidence of perinatal/neonatal death, admission to NICU, 1- and 5-min Apgar <7, number of neonates transfused, postnatal follow-up, and the rate of placental abnormalities.

Statistical Analysis

The Cochrane handbook for systematic reviews of interventions, version 5.1.0 (update March 2011) [18] was followed for systematic review of observational studies. Statistical analysis was

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Table 1. FMH treated with IUT followed by delivery within 72 h

First author [Ref.], year	Age, years	GA at admission, weeks + days	Presenting signs/ symptoms at admission	Confirmation of FMH	Intrauterine transfusion					GA at delivery, weeks + days	Gender	Mode of delivery	Indication for delivery	Neonatal weight, g	Hb/Hct, g/dL/%	Neonatal trans-fusion	Neonatal complications
					estimated fetal blood loss, mL	GA, weeks + days	volume transfused, mL	Hb pre, g/dL	Hct pre, %								
Rouse [20], 1990	28	33+5	FH	FH	230	33+5 34+0	185 130	2.2 5.4	6.5 16	34+1	F	UCS	Persistent FMH	2,380	3.7/11	Yes	Cardiomegaly, hepatitis
Elliott [21], 1991	31	30+3	DFM Sinusoidal FHR	KB test pos.	150	30+3	100	3.2	12.1	30+3	NR	UCS	Prolonged bradycardia	1,760	NR/38	Yes	HMD, hyperbilirubinemia
Elliott [21], 1991	33	31+5	DFM Sinusoidal FHR	KB test pos.	65	31+5	40	2.4	7.0	31+5	NR	UCS	Prolonged bradycardia	1,480	NR/NR	Yes	Mild RSD, moderate hearing loss
Baschat [22], 1998	37	29+3	Sinusoidal FHR ↑ MCA-PSV UC	KB test pos.	180	29+3 29+3[a]	50 NR	NR NR	<11 NR	29+4	NR	UCS	NRFHR DFM	1,250	NR/NR	Yes	IVH, moderate RDS
Weisberg [23], 2004	27	36	FH DFM Sinusoidal FHR ↑MCA-PSV	KB test pos.	288	36	130	2.7	NR	36+1	F	PCS	Planned decision with parents	2,540	12.8/NR	No	No
Amann [24], 2011	NR	NR	↑MCA-PSV	KB test pos.	NR	29+1 29+3 29+4	NR NR NR	3.3 4.3 7.3	NR NR NR	29+4	NR	NR	Significant Hb drop	1,255	15.1/NR	No	NR
Amann [24], 2011	NR	NR	FH ↑MCA-PSV	KB test pos.	NR	29+2 29+3	NR NR	3.1 5	NR NR	29+3	NR	NR	Significant Hb drop	1,570	8.0/NR	Yes	NR
Amann [24], 2011	NR	NR	↑MCA-PSV	KB test pos.	NR	29+6 30	NR NR	6.5 11.3	NR NR	30	NR	UCS	Bradycardia	1,490	12.6	Yes	NR

DFM, decreased fetal movements; FH, fetal hydrops; FHR, fetal heart rate; GA, gestational age; Hb, hemoglobin; Hct, hematocrit; HMD, hyaline membrane disease; IVH, intraventricular hemorrhage; KB, Kleihauer-Betke; MCA-PSV, middle cerebral artery peak systolic velocity; NR, not reported; NRFHR, nonreassuring fetal heart rate; pos., positive; UC, uterine contractions; UCS, unplanned cesarean section; PCS, planned cesarean section; RDS, respiratory distress syndrome. [a] The second IUT was performed 5 h after the first with the intention of further raising the fetal hematocrit.

Table 2. Maternal characteristics

First author [Ref.], year	Age, years	Gravidity and parity	Blood group	Antibody screen	Genetic testing	Infection screening	Hemoglobinopaties	Pregnancy course	Karyotype	MSAFP at admission, ng/ml[a]
Cardwell [25], 1988	24	G3 P1011	0, Rh-positive	Neg	NR	Neg	Neg	Normal	NR	NR
Tannirandorn [26], 1990	32	G1 P0	A, Rh-positive	Neg	NR	Neg	Neg	Normal	NR	483
Fischer [27], 1990	34	G1 P0	0, Rh-positive	Neg	Amniocentesis at 16 weeks	Neg	NR	First-trimester vaginal bleeding	NR	13,473 (normal <430)
Thorp [28], 1992	26	G3 P1011	0, Rh-positive	Neg	NR	Neg	NR	Normal	46,XX[b]	NR
Kohlenberg [29], 1994	36	G2 P1001	0, Rh-positive	Neg	Amniocentesis at 15 weeks	Neg	Neg	Normal	46,XX[c]	NR
Montgomery [30], 1995	26	G1 P0	A, Rh-positive	Neg	NR	Neg	NR	Normal	46,XX[c]	NR
Lipitz [31], 1997	29	G1 P0	0, Rh-positive	Neg	NR	NR	NR	Normal	NR	NR
Hartung [32], 2000	35	G1 P0	B, Rh-positive	Neg	NR	NR	NR	Normal	46,XX[b]	NR
Rubod [16], 2006	34	G5 P4004	A, Rh-positive	NR	NR	Neg	Neg	Normal	46,XX[b]	NR
Votino [33], 2008	33	G1 P0	0, Rh-positive	Neg	NR	Neg	Neg	Normal	46,XX[b]	NR
Sifakis [34], 2010	37	G5 P2113	Blood type NR, Rh-positive	NR	Amniocentesis at 16 weeks	Neg	Neg	Normal	46,XX[c]	NR
Friszer [35], 2010	26	G2 P1001	NR	Neg	NR	Neg	Neg	1.4 g proteinuria/24 h at 28 weeks	NR	NR
Stefanovic [36], 2013	34	G1 P0	AB, Rh-positive	Neg	NR	Neg	Neg	Normal	NR	NR
Our case, 2017	33	G3 P2002	A, Rh-negative	Pos[d]	NIPT neg	Neg	Neg	Fever at 30 weeks	Not done	Not done
Mean ± SD	31.3±4.3									

MSAFP, maternal serum alpha fetoprotein; Neg, negative; NIPT, noninvasive prenatal test; NR, not reported; SD, standard deviation. [a] The values were not recorded as MoM. [b] Karyoptype obtained from fetal blood. [c] Karyotype obtained from amniotic fluid. [d] For anti-D s/p Rhogam administration.

performed for continuous variables by calculating the median or the mean and standard deviation. Categorical outcomes were reported as percentages.

Results

A total of 22 cases of FMH treated with IUT were identified. No randomized controlled trials were identified. Eight cases of FMH (Table 1) were excluded from our review because delivery occurred within 72 h from the first IUT [20–24].

Maternal characteristics of the 14 cases of FMH with subsequent follow-up of at least 72 h are noted in Table 2 [16, 25–36]. Mean maternal age was 31.3 ± 4.3 years, and 50% (7/14) of patients were nulliparous. Karyotype was performed on 7 fetuses (all normal). Cell-free fetal DNA was reported for only 1 patient, and it was normal. Work-up for infection was reported negative in 12 patients screened. Hemoglobinopathy screening was done on 9

Table 3. Features at admission

First author [Ref.], year	GA onset of signs/ symptoms	Presenting signs/symptoms	GA at admission, weeks + days	Ultrasound			MCA-PSV, cm/s (MoM)	Indication for cordocentesis	KB test	Estimated volume of FMH, mL	NST
				AF	FH	other features					
Cardwell [25], 1988	21	Asymptomatic	21	Polyhydramnios	Yes	Placentomegaly	NR	KB test	Pos	20	NR
Tannirandorn [26], 1990	27+4	DFM	28	Polyhydramnios	Yes	Placentomegaly	NR	KB test	Pos	113	Normal
Fischer [27], 1990	29	DFM for 2 weeks and AFM for 3 days	31	Normal	No	Enlarged fetal liver, normal placenta	NR	KB test	Pos	180	Sinusoidal FHR
Thorp [28], 1992	26	Asymptomatic	26	NR	Yes	Placentomegaly	NR	KB test	Pos	100	Poor variability and intermittent prolonged decelerations
Kohlenberg [29], 1994	26	DFM	26+2	Normal	No	AFM, large placental venous lake	NR	KB test	Pos	50	130 FHR with reduced variability
Montgomery [30], 1995	27	Uterine size greater than GA	27	Polyhydramnios	Yes	NR	NR	KB test	Pos	300	NR
Lipitz [31], 1997	27	Abdominal trauma	27	Normal	No	Normal BPP, normal placenta	NR	KB test	Pos	250	Normal
Hartung [32], 2000	28	Asymptomatic	28	NR	Yes	Thickened placenta	NR	FH	Pos	250	NR
Rubod [16], 2006	28+2	DFM	28+5	NR	Yes	Placental edema	77 (2.10)	FH and sinusoidal FHR	Pos	240	140 FHR with isolated decelerations
Votino [33], 2008	25+5	DFM	26+5	NR	Yes	Placental edema	73 (2.16)	KB test	Pos	90	Very low short-term variability and no accelerations
Sifakis [34], 2010	24	Asymptomatic	24	Polyhydramnios	Yes	Placental edema	84 (2.73)	KB test	Pos	32	NR
Friszer [35], 2010	28	Asymptomatic, proteinuria	29+2	NR	Yes	NFM	71 (1.83)	KB test	Pos	75	Normal
Stefanovic [36], 2013	26+5	DFM	27+1	Reduced	No	AFM	55 (1.55)	LCM pos	Pos	>80	Sinusoidal FHR with variable decelerations
Our case, 2017	29+6	DFM	31+5	Normal	No	Fetal ascites and hepatomegaly	63.4 (1.48)	KB test, increased MCA-PSV	Pos	35	Nonreactive
Mean ± SD	26.6±2.1		27.1±2.4				70.6±10.7 (1.95±0.45)			129.6±94.9	

AF, amniotic fluid; AFM, absent fetal movements; BPP, biophysical profile; DFM, decreased fetal movements; FH, fetal hydrops; FHR, fetal heart rate; Ga, gestational age; KB, Kleihauer-Betke; LCM, liquid chromatography method; MCA-PSV, middle cerebral artery peak systolic velocity; NFM, normal fetal movements; NST, nonstress test; NR, not reported; Pos, positive; SD, standard deviation.

patients, and results were negative. One case had a febrile illness at 30 weeks with a negative parvovirus infection workup.

The gestational age at the onset of signs and/or symptoms was 26.6 ± 2.1 weeks, and the gestational age at admission was 27.1 ± 2.4 weeks (Table 3). Indications for referral were: decreased fetal movements alone (35.7%, 5/14), fetal hydrops alone (28.6%, 4/14), fetal hydrops plus decreased fetal movements (14.3%, 2/14), fetal hydrops plus proteinuria (7.1%, 1/14), maternal abdominal trauma (7.1%, 1/14), and uterine size greater than gestational age (7.1%,1/14). Five patients (35.7%) were asymptomatic and signs of fetal hydrops were revealed only with routine ultrasound evaluation. Ultrasound assessment at admission showed fetal hydrops in 64.3% (9/14), abnormal placental size in 53.8% (7/13) and polyhydramnios in 44.4% of patients (4/9). The MCA-PSV at admission was available in 6 patients; the mean of multiple of the medians (MoM) was 1.95 ± 0.45. FMH was confirmed by laboratory testing in all cases (13 with Kleihauer-Betke test and 1 with liquid chromatography method). The mean estimated volume of FMH was 129.6 ± 94.9 mL. The decision to perform cordocentesis was triggered by a positive Kleihauer-Betke test in 78.6% (11/14). NST upon admission was described in 10 patients and was categorized as nonreactive, with reduced variability and decelerations in 5 (50%), normal in 3 (30%), and sinusoidal in 2 (20%).

A total of 39 successful IUTs were performed (Table 4) on the 14 patients. The first IUT was performed at 27.1 ± 2.4 weeks, and this occurred 4.5 ± 4.3 days from the onset of sign/symptoms suggestive of FMH. The detection of fetal anemia before the first IUT was triggered most by the following features: fetal hydrops plus positive laboratory testing (42.8%, 6/14) and decreased fetal movements

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Table 4. Intrauterine transfusions

First author [Ref.], year	Intrauterine transfusion											Monitoring
	IUT, *n*	GA, weeks + days	MCA-PSV before IUT, cm/s (MoM)	MCA-PSV after IUT, cm/s (MoM)	indication	Hb pre, g/dL	Hct pre, %	Hb post, g/dL	Hct post, %	transfused volume, mL	total volume transfused in all IUTs, mL	
Cardwell [25], 1988	1	21	NR	NR	FH with KB test pos.	NR	NR	NR	NR	50[a]	50	Serial KB testing and US
Tannirandorn [26], 1990	1	28[b] 29	NR	NR	DFM with KB test pos. Scheduled, no fetal anemia, no IUT[d]	5.8 12.6	17.2 37	NR	36.7	65[c] 0	65	NR
Fischer [27], 1990	2	31 31+5	NR	NR	DFM with KB test pos. DFM and sinusoidal FHR	2.2 4.2	7.6 13.5	12.4 12.2	39.2 37.9	96 100	196	NR
Thorp [28], 1992	2	26 27 29	NR	NR	Massive FH with KB test pos. DFM and sinusoidal FHR Scheduled, no fetal anemia, no IUT[d]	2.7 9.8 14.1	7 28 41	14.2 13.8	42 42	75 35 0	110	Twice weekly US, twice weekly NST, weekly KB testing
Kohlenberg [29], 1994	2	26+2 26+6 30 33	NR	NR	DFM with KB test pos. Scheduled, fetal anemia, no IUT[d] DFM with KB test pos. Scheduled, no fetal anemia, no IUT[d]	2.7 8.4 3.7 10.6	NR NR NR NR	8.3 11.3 	NR NR 	35 0 50 0	85	Daily fetal movement count and NST, serial KB testing
Montgomery [30], 1995	5	27 27+5 29 29+5 30+2	NR	NR	Fetal anasarca with KB test pos. KB test pos. Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d] Scheduled, no fetal anemia, IUT[d]	5.5 6.1 6.1 8 11.1	16.4 18 18 23.7 32.7	NR NR NR NR NR	28.5 28 31.5 34.8 40.3	26 40 46+80† 35+20† 22	269	Biweekly BPP
Lipitz [31], 1997	1	27+5	NR	NR	KB test pos. for a week	8.8	26	NR	40.6	30	30	Weekly KB testing
Hartung [32], 2000	5	28 28+2 29 to 31	NR	NR	FH FH 3 scheduled, anemia NR, IUT[d]	4 NR NR	NR NR NR	7.6 10.4 NR	NR NR NR	40 50 NR	Not possible to estimate	Daily US and NST, weekly cordocentesis
Rubod [16], 2006	2	28+6 30 31+3	77 (2.10) 60 (1.48) 48 (1.13)	NR NR	FH, sinusoidal FHR, AFM DFM and sinusoidal FHR Scheduled, no fetal anemia, no IUT[d]	2.2 4.4 11.7	NR NR NR	9.9 11.8	NR NR	140 162 0	302	Fetal movement count, twice daily NST, twice a week MCA-PSV
Votino [33], 2008	4	26+5 27+3 29+3 29+6 33+1	73 (2.16) NR 80 (2.06) NR 52 (1.10)	NR NR 51 (1.31) NR	FH with KB test pos. Scheduled, anemia NR, IUT[d] DFM and sinusoidal FHR Scheduled, fetal anemia, IUT[d] DFM	2.9 NR 3.7 7.7 NR	7 NR 10 23 NR	NR 12.4 9.4 NR	41 37 27 50	83 40 86 62 0	271	Fetal movement count, twice daily NSTand daily MCA-PSV
Sifakis [34], 2010	8	24+5 24+6 25 25+3 25+3 26 26+5 27+2	84 (2.73) NR 52 (1.61) 42 (1.30) 64 (1.99) 59 (1.75) 53 (1.57) 41 (1.16)	41.2 (1.34) 49.2 (1.60) NR NR 49 (1.52) 43.9 (1.30) 37.8 (1.12) NR	Severe FH with KB test pos. Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d] Scheduled, fetal anemia, IUT[d]	2.5 2.5 5.7 1.3 8.3 5 6.4 8.5	NR NR NR NR NR NR NR NR	5.6 6.2 6.9 8.3 10.8 8.8 9.2 9.8	NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR	350	NR
Friszer [35], 2010	3	29+3 30+4 31+4	71 (1.83) 80 (1.88) 66 (1.50)	55 (1.42) 35 (0.82) 35 (0.82)	Severe FH with KB test pos. ↑MCA-PSV ↑MCA-PSV	4.5 4.2 6.3	NR NR NR	12.5 16.2 15.5	NR NR NR	NR NR NR	NR	Twice daily NST and daily MCA-PSV
Stefanovic [36], 2013	2	27+2 28	55 (1.55) 77 (2.08)	NR NR	DFM with LCM pos. DFM and sinusoidal FHR	1.8 3.2	NR	11.9 10.5	NR	35 40	75	NR
Our case, 2017	1	32+1	63.4 (1.48)	42.8 (0.95)	DFM, KB test pos., fetal ascites and ↑MCA-PSV	6.1	21.6	13.1	44.6	35	35	Twice weekly NST, MCA-PSV and hydrops checks
Total	39											

AFM, absent fetal movements; BPP, biophysical profile; DFM, decreased fetal movements; FH, fetal hydrops; FHR, fetal heart rate; GA, gestational age; Hb, hemoglobin; Hct, hematocrit; IUT, intrauterine transfusion; KB, Kleihauer-Betke; LCM, liquid chromatography method; MCA-PSV, middle cerebral artery peak systolic velocity; NST, nonstress test; NR, not reported; Pos, positive; US, ultrasound. [a] Intraperitoneal transfusion. [b] After IUT, onset of maternal hypertension with 3+ proteinuria. [c] Intrahepatic vein transfusion. [d] Cordocentesis was done based on the preference of the providers with no worsening of signs or symptoms.

Table 5. Characteristics of successive IUTs

	Patients	Hb pre, g/dL	Hct pre, %	Hb post, g/dL	Hct post, %	MCA-PSV pre, MoM	MCA-PSV post, MoM	Volume transfused, mL	Time interval between IUTs, days	Symptomatic patients
First IUT	14 (100)	4.0±2.1	14.7±7.7	10.6±2.9	38.9±5.2	1.95±0.45	1.24±0.25	59.2±35.0	NA	7/14 (50)
Second IUT	10 (71.4)	4.8±2.3	19.8±7.4	11.6±2.7	36.2±5.9	1.81±0.30	1.21±0.55	64.6±44.5	7.2±7.0	6/10 (60)
Third IUT	5 (35.7)	5.4±1.2	23.0±16.1	10.6±4.4	29.2±3.2	1.72±0.30	1.06±0.34	106.0±64.4	7.2±4.8	1/5 (20)
Fourth IUT	4 (28.6)	5.7±3.8	23.3±0.5	8.3[a]	42.4±10.7	1.3[a]	NR	58.5±33.9	4.5±1.9	0/4 (0)
Fifth IUT	3 (21.4)	9.7±2.0	32.7[a]	10.8[a]	40.3[a]	1.99[a]	1.52[a]	22[a]	2.0±2.8	0/3 (0)
Sixth IUT	1 (7.1)	5	NR	8.8	NR	1.75	1.30	NR	4	0/1 (0)
Seventh IUT	1 (7.1)	6.4	NR	9.2	NR	1.57	1.12	NR	5	0/1 (0)
Eighth IUT	1 (7.1)	8.5	NR	9.8	NR	1.16	NR	NR	4	0/1 (0)

Data are presented as total number of patients (%) or as mean ± SD. NR, not reported; Hb, hemoglobin; Hct, hematocrit; IUT, intrauterine transfusion; MCA-PSV, middle cerebral artery peak systolic velocity; NA, not available. [a] Data are available for only 1 patient.

plus positive laboratory testing (28.6%, 4/14). The fetal hemoglobin and hematocrit before the first IUT were 4.0 ± 2.1 g/dL and 14.7 ± 7.7%, respectively; after the procedure, they were 10.6 ± 2.9 g/dL and 38.9 ± 5.2%, respectively (Table 5). The mean transfused volume was 59.2 ± 35.0 mL. The MCA-PSV measurements before and after the transfusion were 1.95 ± 0.45 MoM (available for 6 of the 14 patients) and 1.24 ± 0.25 MoM (available for only 3 of the 14 patients).

The second IUT was performed in 10 cases (71.4%) with a time interval from the first IUT of 7.2 ± 7.0 days, and the mean transfused volume was 64.6 ± 44.5 mL (available for 8 of the 10 patients). The fetal hemoglobin and hematocrit before the second IUT were 4.8 ± 2.3 g/dL and 19.8 ± 7.4%, respectively; after the procedure, these values were 11.6 ± 2.7 g/dL and 36.2 ± 5.9%, respectively. The MCA-PSV values were available only in few cases and were 1.81 ± 0.30 MoM (3 out of 10 cases) and 1.21 ± 0.55 MoM (2 out of 10 cases) before and after the procedure (Table 5). The detection of the recurrence of fetal anemia after the first IUT was triggered by the following features: decreased fetal movements plus sinusoidal pattern (40%, 4/10), scheduled cordocentesis without symptoms (20%, 2/10), decreased fetal movements plus Kleihauer-Betke test positive (10%, 1/10), Kleihauer-Betke test positive alone (10%, 1/10), recurrence of fetal hydrops (10%, 1/10), and increased MCA-PSV (10%, 1/10) (Table 4). A second cordocentesis without IUT was performed in only 2 cases; these patients were asymptomatic, and fetal hemoglobin was 12.6 and 8.4 g/dL.

Five patients (35.7%) underwent a third IUT with a time interval from the second of 7.2 ± 4.8 days and a mean transfused volume of 106.0 ± 64.4 mL (available for only 2 of the 5 patients). The fetal hemoglobin and hematocrit before the third IUT were 5.4 ± 1.2 g/dL and 23 ± 16.1%, respectively; after the procedure, these values were 10.6 ± 4.4 g/dL and 29.2 ± 3.2%, respectively. The MCA-PSV values were 1.72 ± 0.30 MoM before the IUT (4 out of 5 cases) and 1.06 ± 0.34 MoM (2 out of 5 cases) after the procedure (Table 5). The most common indication for the third IUT was scheduled cordocentesis without symptoms (60%, 3/5) (Table 4).

The fourth and fifth IUTs were performed for 4 (28.6%) and 3 (21.4%) patients, respectively, after 4.5 ± 1.9 days from the third IUT and 2.0 ± 2.8 days from the fourth IUT. The fetal hemoglobin and hematocrit before the fourth IUT were 5.7 ± 3.8 g/dL and 23.3 ± 0.5%, respectively; after the procedure, these values were 8.3 g/dL (1 out of 4 cases) and 42.4 ± 10.7% (2 out of 4 cases), respectively. In only 1 patient, another 3 IUTs were carried out 4 or 5 days apart from each other (Table 5).

In 8 patients, cordocentesis was performed for no presenting signs or symptoms, but seemingly only for the physician's preference and absent abnormal ultrasound findings or nonreassuring fetal testing. In 4 (50%) of these 8 patients, fetal anemia was detected, 3 of which had IUT (Table 4).

After the first successful IUT, monitoring was reported in 10 cases (71.4%) and included: serial Kleihauer-Betke testing (4 cases); NST twice daily (3 cases), daily (2 cases) or twice weekly (2 cases); daily fetal movement count (3 cases); MCA-PSV daily (2 cases) or twice weekly (2 cases); biophysical profile twice weekly (1 case); ultrasound evaluation twice weekly (2 cases), daily (1 case) or serially (1 case); weekly cordocentesis (1 case) (Table 4).

The mean gestational age at delivery was 34.2 ± 4.2 weeks, and the time interval between the first IUT and delivery was 53.6 ± 54.8 days (Table 6). A cesarean section

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Table 6. Neonatal characteristics

First author [Ref.], year	GA at delivery, weeks + days	Days since first IUT and delivery	Gender	Mode of delivery	Indication	Outcome	Apgar score[a]	Weight, g	Hb, g/dL	Hct, %	Assisted ventilation	Neonatal transfusion	NICU course	Postnatal follow-up
Cardwell [25], 1988	38+4	193	F	PCS	Previous CS	Alive	NR	2,750	17.2	51.3	NR	No	NR	NR
Fischer [27], 1990	31+6	6	NR	UCS	Sinusoidal FHR and breech	Alive	9/10	1,750	6.6	20.6	No	Yes, twice	Phototherapy for hyperbilirubinemia	Normal
Thorp [28], 1992	39	91	F	VD	Spontaneous onset of labor	Alive	9/9	3,263	17.1	52	No	No	Uncomplicated	Normal at 8 weeks
Kohlenberg [29], 1994	38	82	F	CS	NR	Alive	NR	NR	15.5	NR	No	No	Uncomplicated	NR
Montgomery [30], 1995	30+4	25	M	CS	Maternal fever, uterine contractions and breech	Alive	4/8	1,740	18.2	56.7	Yes	No	Uncomplicated	NR
Lipitz [31], 1997	39	79	F	VD	PROM	Alive	9/10	2,800	13.9	41	No	No	Uncomplicated	NR
Hartung [32], 2000	31	21	F	CS	NR	Alive	7/9	1,850	10.2	28	Yes	Yes, once	Phototherapy for hyperbilirubinemia	Normal at 1 year
Rubod [16], 2006	38	64	M	PCS	Breech	Alive	10/10	3,400	14.2	NR	No	No	Uncomplicated	Normal at 1 month
Votino [33], 2008	33+1	45	F	CS	DFM and suspected recurrent FMH	Alive	10/10	2,075	13.6	46	No	No	Uncomplicated	Normal at 8 months
Friszer [35], 2010	31+5	16	F	UCS	Rapid increase in MCA-PSV	Alive	8/7	1,530	10.2	NR	Yes	Yes, once	Uncomplicated	Normal at 6 months
Stefanovic [36], 2013	28+2	7	F	PCS	Planned	Alive	3/NR	1,060	6.0	NR	Yes	Yes, four times	Uncomplicated	Normal at 2 years
Our case, 2017	34+1	14	F	PCS	Previous CS	Alive	7/9	2,280	17.3	52.1	No	No	Uncomplicated	Normal at 3 months
Mean ± SD	34.2± 4.2	53.6± 54.8						2,227.1± 743.7	13.3± 4.2	43.5± 12.9	4[b]	4[b]		

CS, cesarean section; DFM, decreased fetal movements; F, female; FHR, fetal heart rate; GA, gestational age; Hb, hemoglobin; Hct, hematocrit; IUT, intrauterine transfusion; M, male; MCA-PSV, middle cerebral artery peak systolic velocity; NICU, neonatal intensive care unit; NR, not reported; PCS, planned cesarean section; PROM, premature rupture of the membranes; UCS, unplanned cesarean section; VD, vaginal delivery. [a] Reported at 1 and 5 min after birth. [b] Total.

Table 7. Placental characteristics

First author [Ref.], year	Histological abnormalities	Hydropic changes/ placentomegaly	Nucleated red blood cells within villous capillaries	Fibrous lesions	Chorioangiosis	Placental abruption	Thrombosis of fetal vessels	Retroplacental hematomas	Chorioamnionitis	Defect on the chorionic epithelium
Cardwell [25], 1988	No	No	No	No	No	No	No	No	No	No
Tannirandorn [26], 1990	Yes	Yes	No	No	No	No	No	No	No	No
Fischer [27], 1990	Yes	No	No	No	No	Yes	Yes	Yes	No	No
Thorp [28], 1992	No	No	No	No	No	No	No	No	No	No
Kohlenberg [29], 1994	Yes	No	No	Yes	No	No	No	No	No	No
Montgomery [30], 1995	Yes	Yes	No	No	No	No	No	No	No	No
Hartung [32], 2000	Yes	No	No	No	No	No	No	No	No	Yes
Rubod [16], 2006	No	No	No	No	No	No	No	No	No	No
Votino [33], 2008	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No
Sifakis [34], 2010	Yes	No	Yes	No	No	No	No	No	Yes	No
Friszer [35], 2010	No	No	No	No	No	No	No	No	No	No
Stefanovic [36], 2013	Yes	No	Yes	No	No	No	No	No	No	No
Our case, 2017	No	No	NR	No	No	No	No	No	No	No
Total	8/13	3/13	2/13	2/13	1/13	1/13	2/13	1/13	1/13	1/13

NR, not reported.

was performed in 10 patients (71.4%) and spontaneous vaginal birth occurred in 3 cases (21.4%).

There were 2 cases of fetal demise (14.3%). The first was at 30 weeks after 1 IUT; placental pathology revealed hydropic changes and autopsy showed no specific abnormality of the infant [26]. The second was at 28 + 2 weeks after 8 IUTs; hypoxic-ischemic damage of the brain and multiorgan inflammatory infiltrates were reported on autopsy, and placental pathology revealed hydropic changes, diffuse placentitis with chronic villitis and chorioamnionitis [34]. The hemoglobin prior to the first IUT was 5.8 and 2.5 g/dL, respectively, and in both cases fetal hydrops and polyhydramnios were present. The estimated fetal blood loss was 113 and 32 mL, respectively. Fetal death occurred 14 and 7 days after the last IUT, respectively.

Regarding neonatal outcomes (Table 6), the mean Apgar scores at 1 and 5 min were 7.6 ± 2.4 and 9.1 ± 1.1, respectively, and the mean birth weight was 2,227.1 ± 743.7 g. Neonates had an initial hemoglobin of 13.3 ± 4.2 g/dL and hematocrit of 43.5 ± 12.9%. Four out of 12 neonates (33.3%) were transfused after birth. Hyperbilirubinemia treated with phototherapy was required for 2 neonates (16.7%). Follow-up was available for 8 (66.7%) neonates (range 1 month to 2 years), and all infants were reported to be in good condition with a normal neurological status (Table 6). No neonatal deaths occurred.

Placental characteristics were available in 13 cases, and histological abnormalities were reported in 61.5% (8/13) (Table 7). The features described included placental hydropic changes/placentomegaly (23.1%, 3/13), nucleated erythrocytes within villous capillaries (15.4%, 2/13), fibrous lesions (15.4%, 2/13), thrombosis of the fetal vessels (15.4%, 2/13), placental abruption (7.7%, 1/13), and retroplacental hematoma (7.7%, 1/13) among others. No neoplastic features, placenta or vasa previa, anomalous cord insertion, or placental infarcts were reported.

Discussion

Our systematic review retrieved 14 cases of FMH with proven fetal anemia treated with IUT who had subsequent follow-up of >72 h. Our data demonstrate a 71.4% recurrence rate of FMH after the first IUT. The FMH recurrence necessitated a second IUT about 7 days after the first IUT procedure. The recurrence of FMH continued after the second IUT with progressive reduction in time between transfusions.

Cases of FMH with proven fetal anemia usually presented with either fetal hydrops or decreased fetal movements in the late second trimester. Most cases had fetal hydrops on ultrasound, and these findings were often incidental, so the diagnosis of FMH should be considered in the workup of nonimmune hydrops. It is surprising that maternal history of trauma that could be associated with FMH was absent in all patients, except 1 [31]. All FMH cases were confirmed by either the Kleihauer-Betke or the liquid chromatography method. The MCA-PSV recorded at admission in our cases with signs/symptoms of proven fetal anemia was abnormal in all cases, except 1. This confirms that MCA-PSV is a good indicator of severe fetal anemia independent of the etiology [14, 37, 38]. Furthermore, the mean value of MCA-PSV before each new episode of FMH was increasingly lower from the first to the third IUT. The sensitivity and specificity of this technique may be excellent for the first IUT but may not be as sensitive in guiding timing of the subsequent procedures [39]. Several authors studied MCA-PSV value in the aftermath of a first IUT [35, 40]. After an initial transfusion, the Society for Maternal-Fetal Medicine recommends higher threshold (MoM >1.69) for the diagnosis of fetal anemia requiring a second transfusion [19]. The 1.69 cutoff as suggested by the Society for Maternal-Fetal Medicine would not have identified all the anemic fetuses that received the second and third IUTs.

A majority had a second episode of FMH requiring subsequent IUTs, typically within 1 week. IUT is a well-established method to correct fetal anemia and prolong gestation until a more mature gestational age is reached [17]. Our review confirms that the management strategy of IUTs for FMH resulted in significant gains in gestational age, although multiple transfusions were typically needed. Fetal demise occurred in 2 patients (14%) [26, 34]. In general, these 2 cases of fetal demises were associated with very severe fetal anemia at presentation (hemoglobin <6 g/dL). No neonatal deaths were recorded and the successful IUTs led to a mean neonatal hemoglobin of 13.3 ± 4.2 and a 33% rate of neonatal transfusion.

Given the need for serial IUTs for recurrent fetal anemia and the risk of fetal demise, fetal monitoring is of paramount importance. As the data are limited, and each case was followed with somewhat different fetal monitoring schedules, proposing a specific monitoring plan based on this review is challenging. In general, we suggest at least 2–3 times a week ultrasound examination (for hydrops assessment, biophysical profile, and MCA-PSV) and NST daily or twice daily. In fact, given the frequency and severity of the FMH recurrences, inpatient daily monitoring should be considered. The timing of planned delivery could reasonably be around 34 weeks, or even earlier if frequent FMH recurrences more than weekly are seen, steroids have been given, and the gestational age is >30 weeks. These management decisions should be via shared decision making involving a multidisciplinary approach with the goal of minimizing fetal and neonatal complications.

The long-term neurodevelopmental outcome of children born after IUT for red cell alloimmunization is considered to be favorable, and severe hydrops has been identified as a strong predictor of neurodevelopment impairment [41]. However, the long-term outcome of survivors of IUT for FMH is not well known [41, 42]. Follow-up studies are limited by small sample sizes, lack of controls and lack of established criteria for the diagnosis of neurodevelopment delay. Our data of long-term outcome after FMH treated with IUT revealed the same limitations.

The placental pathology in our review revealed histological abnormalities in 61.5% of the cases, with a wide spectrum of pathological changes. Intervillous thrombosis and increased nucleated red blood cells have been described in fetal and neonatal deaths due to FMH: the first feature was present in half of the cases, while the second was almost always present [43, 44]. High rate of placentomegaly (41%) was also reported [43]. Ravishankar et al. [45] demonstrated that some macro- and microscopic placental pathology parameters, such as parenchymal pallor, intervillous thrombi, and increased nucleated red blood cells, are significantly higher in placentas with FMH, which was confirmed by the Kleihauer-Betke test, both in liveborns and stillborns. Although our limited data reveal a reduced incidence of these features, it is difficult to establish if the treatment of FMH with IUTs is able to reduce these placental features. However, no other data on placental histological characteristic of FMH patients treated with IUTs are currently available.

The strengths of our study include that it is the first systematic review, to our knowledge, to review all cases of

FMH with proven fetal anemia treated with IUT and who had subsequent follow-up of >72 h. Therefore, we were able to estimate for the first time the rate of recurrence of FMH.

The limitation of our study is the nature of a systematic review and the limited information within the published cases. The only publications examining monitoring of FMH cases treated with IUTs were case reports. Publication bias may certainly be present, probably favoring successful cases. The frequency and number of IUTs analyzed in this review may be an overestimation of the rates of recurrence and need for IUT.

In addition, we assumed that anemia after IUT is due to recurrence of FMH and not other causes. This is likely correct as other etiologies of the original anemia were evaluated and not found, and the recurrence of anemia within a short timeframe made it unlikely that another cause of anemia would have occurred.

Expectantly managed FMH patients with proven fetal anemia treated with IUT and subsequent follow-up of >72 h have a 71% rate of recurrence, and 14% rate of fetal demise. Once the diagnosis is confirmed by signs/symptoms and a positive maternal laboratory exam, MCA-PSV should be used to evaluate for severe fetal anemia. Given the high rate of recurrence of FMH, usually within 1 week of IUT, we suggest ultrasound examination at least 2–3 times a week and NST daily or twice daily with inpatient management.

Conclusion

Massive FMH can cause devastating pregnancy outcomes. Although the recurrence rate of FMH was high, IUT is a safe and effective tool to improve fetal and neonatal outcomes. Most fetuses will require at least 2 IUTs to achieve an advanced gestational age. Close monitoring of these patients is necessary to recognize the early signs and symptoms of FMH recurrence. However, further research is required in order to standardize pregnancy management protocol including timing of delivery.

Disclosure Statement

The authors report no conflict of interests.

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