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Fetal Intrauterine Transfusion Therapy: Neonatal Outcomes

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Abstract

Background and objectives: Intrauterine blood transfusion (IUT) performed for fetal anemia may be associated with adverse neonatal outcomes. This study aimed to describe the clinical outcome of surviving neonates treated with IUT in an area where detailed outcome on neonatal data is limited.

Patients and methods: This prospective study included all living newborns treated with IUT at our institution between March 2004 and February 2011. During this period, 30 newborns with a mean gestation age of 35 weeks (range: 25-37 weeks) were admitted with various respiratory, hematological and gastrointestinal morbidities.

Results: The survival rate on discharge was 93%. Severe fetal anemia (72.2%) was significantly associated with a low reticulocyte count at birth and the need for respiratory support after birth (P<0.05). The number of IUTs was significantly correlated with the duration of admission (P=0.034) and the presence of hyporegenerative late anemia (P=0.007), but not with other neonatal outcomes or with a low reticulocyte count at birth. Use of intravenous immunoglobulin was significantly associated with an increased rate of top-up transfusion for late anemia and a decreased duration of admission, with no additional positive effects.

Conclusion: This study provides evidence on the types of potential neonatal morbidities after IUT therapy and their risk factors, and could be useful to clinicians treating fetuses with intrauterine transfusions and also for counseling parents.

Keywords: Neonatal outcome; Intrauterine transfusion; Fetal anemia; Intravenous immunoglobulin; Late anemia

Abbreviations: IUT: Intrauterine Transfusion; MCA-PSV: Middle Cerebral Artery Peak Systolic Velocity; IVIG: Intravenous Immunoglobulin; HB: Hemoglobin; GA: Gestation Age; ET: Exchange Transfusion

Introduction

Fetal anemia is a major problem and cause of neonatal morbidities and mortalities. Fetal anemia can be detected reliably by noninvasive measurements of the Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) [1]. Rodeck et al. performed the first Intrauterine blood Transfusion (IUT) using the intraperitoneal technique. In the 1980s, this technique was replaced by intravascular IUT [2]. This procedure is currently performed through single or repeated direct intravascular injections of red blood cells from an Rh-negative donor through the intrahepatic umbilical vein or the umbilical cord at its placental insertion [3]. Although the use of anti-D prophylaxis has dramatically reduced the need for IUT, the procedure continues to be an essential modality for the treatment of severe fetal anemia from a variety of causes [2]. Because of improvements in obstetric and neonatal management, the perinatal survival rate for babies treated with IUT for alloimmune fetal anemia exceeds 90% [1]. This improved survival rate has resulted in increased attention to the short- and long-term outcomes in surviving children. Information regarding the adverse effects of IUT on detailed neonatal outcome is limited [4]. Outcomes have been reported to be dependent on many factors, including the primary cause and severity of fetal anemia, the severity and reversibility of hydrops at the time of diagnosis, and the time when the therapy was initiated [5-7]. Long-term follow up studies have revealed normal neurologic outcomes in 95% of cases [6]. This article reports on the detailed outcomes of neonates treated with IUT.

Materials and Methods

Participants

This prospective study was conducted at Jordan University Hospital, a tertiary referral center, from March 2004 to February 2011. All newborns that underwent successful intravascular transfusion therapy (via the intrahepatic vein or free umbilical vein in the cord) for fetal anemia (hemoglobin level<10 g/dl) during the study period were included. The diagnosis of fetal anemia was based on serial measurements of the MCA-PSV followed by determination of fetal hematocrit by cordocentesis. IUT was initiated when the fetal Hemoglobin (Hb) level fell below 1.5 multiples of the median [8]. Pancuronium or atracurium was used for all fetuses. One course of antenatal corticosteroids was administered to all women after 24 weeks of gestation. All babies and their mothers were treated by the same staff physicians and underwent standard follow-up examinations. All participant mothers received complete information on the purpose of the study. Informed consent was obtained from each baby's guardian after approval of the study protocol by the institutional human ethical committee and the deanship of scientific research at the University of Jordan. This study was conducted according to principles of the

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Helsinki Declaration. Patients received erythropoietin was excluded from the study (Number=4)

Definitions

Gestational Age (GA) was determined according to the last menstrual period and confirmed by fetal ultrasound in the first trimester. Severe fetal anemia was defined as a cord blood Hb level of less than 5.5 gm/dl and an MCA-PSV<0.55 multiples of the median for a given GA. Non severe fetal anemia (mild to moderate) was defined as a cord blood Hb level between 5.5 and 10 gm/dl and an MCA-PSV<0.84 multiples of the median (mild) or <0.65 multiples of the median (moderate) for a given GA. Hydrops was defined as the presence of accumulated fluid in at least one fetal body cavity (mainly ascites), along with fetal skin edema.

Planned delivery was defined as a planned elective cesarean section without labor or a planned induced vaginal delivery or cesarean section due to failed planned induction. Unplanned delivery was defined as spontaneous vaginal delivery or urgent cesarean section due to maternal or fetal causes.

Vigorous resuscitation at birth was defined as the need for positive pressure ventilation by bag and mask and/or intubation because of an absence of breathing, labored irregular breathing, gasping baby, and/or a heart rate<100 beats/min.

Need for respiratory support after birth was defined as the need for oxygen for more than 24 h via nasal cannula, continuous positive airway pressure, and/or mechanical ventilation. Late anemia was defined as Hb<10 g/dl with an onset between 2 and 6 weeks of life; it was considered hyporegenerative late anemia if it was associated with low reticulocyte counts (<1%) [9]. A top-up transfusion was defined as a blood transfusion in the first 4 months of life. Top-up blood transfusion (20 ml/kg) was performed if Hb<8.0 g⁄dl (or Hb<10 g⁄dl in the presence of clinical symptoms of neonatal anemia).

Phototherapy, Intravenous Immune Globulin (IVIG), and exchange transfusion were performed according to the American Academy of Pediatrics 2004 guidelines [10]. Intensive phototherapy was provided by Mediprema all-around phototherapy and/or a special blue light source (Lullaby™, at a distance of 30-40 cm from the baby with regular changes of position). Neurodevelopmental delay was defined as the presence of at least one of the following: cerebral palsy, cognitive delay, deafness, or blindness.

Family characteristics

Data were collected regarding patients' history of previous intrauterine fetal death, siblings with neonatal death, or siblings who needed phototherapy, Exchange Transfusion (ET), or top-up blood transfusion.

Fetal characteristics

The following fetal data were recorded: GA at which IUTs were administered, number of IUTs, fetal Hemoglobin concentration (HB/hematocrit) as diagnosed by MCA-PSV and cordocentesis before and after IUT, severity of fetal anemia, and evidence of ascites and hydrops.

Neonatal outcomes

Delivery room: Data were collected on the immediate delivery outcome, including mode of delivery, birth weight, gender, GA, Apgar scores at 1 and 5 min, GA percentile, and baby condition at birth, including the presence of shock and the need for vigorous resuscitation at birth.

Immediate post-birth: Immediately post-birth, several variables were recorded: umbilical cord results at birth (including Hb, mean corpuscular volume, reticulocyte count, and baby blood group and Rh), direct Coomb's test, total serum bilirubin, Neonatal Intensive Care Unit (NICU) admission, and the presence of hepatomegaly (liver >4 cm below right costal edge and span >5 cm) and/or splenomegaly (spleen tip>2 cm below costal edge).

Neonatal morbidity during hospitalization: Data were collected on each baby's condition during neonatal hospitalization, including the following factors: Thrombocytopenia and Neutropenia in the first 24 h of life, the need for phototherapy/exchange transfusion, the use of IVIG (administered as 2 doses of 1 g/kg administered over 4 h, initiated in the first 12 h of life and repeated once after 12 h if the bilirubin level continued to rise despite intensive phototherapy or was within 2-3 mg/dl of the threshold for exchange transfusion), hospitalization course (including the need for ongoing respiratory support), echocardiogram findings, presence and duration of cholestasis, duration of hospitalization, and death.

Late anemia: The presence and duration of hyporegenerative late anemia were recorded.

Neurodevelopmental outcome at 12 months: A final physical and Neurodevelopmental examination was performed at 12 months of age, searching for any signs of Neurodevelopmental delay. Brain computed tomography (CT) scan and/or brain Magnetic Resonance Imaging (MRI) were performed if a Neurodevelopmental delay was detected (n=9).

Statistical analysis: Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 17). A P-value of less than 0.05 was regarded as statistically significant. Maternal and neonatal characteristics and outcomes were examined, and data are presented as raw frequencies and adjusted odds ratios with 95% confidence intervals.

Results

Participants

The study included 19 mothers and 30 babies (including 2 sets of twins) with a median GA of 35 weeks (range 25^{+3}-37^{+6} weeks). Of the neonates, 60% were female, 90% had appropriate birth weight for GA (n=27), and 60% were born at ≥ 35 weeks. The median birth weight was 2575 ± 550 g.

Family characteristics

A history of a previously affected fetus/sibling in patients' families was identified in 89.3% of the cases. The main cause of fetal anemia was Rhesus type D isoimmunization in 26 patients (86.7%), an unknown cause in 3 patients (10%), and Rhesus type D/C isoimmunization in 1 patient (3.3%). Among the 19 mothers with Rhesus type D isoimmunization, 11 mothers did not receive anti-D prophylaxis after the first pregnancy/abortion (including 2 mothers whose blood group was not tested and 1 mother who had an incorrect blood group listed at the time of admission). Previous intrauterine fetal deaths were reported in 12 cases (40%), siblings with neonatal deaths in 14 cases (46.7%), siblings who needed exchange after birth in 13 cases (43.3%), siblings who needed phototherapy after birth in 27 cases (90%), and siblings who needed blood top-up transfusion in 16 cases (53.3%).

Fetal characteristics

Eighty IUTs were performed, with a median number of 3 per fetus

(range: 1-4). The earliest therapy was initiated at the age of 21 weeks (median: 25 weeks, range: 21-33 weeks). There was a progressive increase in the mean time interval between the IUTs: The mean time interval between the second and the third IUT was 4 weeks, compared to 3 weeks between the first and second IUTs. The median fetal Hb levels (as diagnosed by cordocentesis) before the first, second, and third IUTs were 5.1, 7.3, and 7 g/dl, respectively. Hemoglobin increased in the fetus by an average of 16 g/dl after each IUT (range: 9-22 g/dl). Severe fetal anemia occurred in 18 cases (60%).

Nine neonates (30%) showed evidence of isolated fetal ascites at the start of IUT, and 2 neonates had hydrops, including ascites with skin edema and plural and pericardial effusion. All cases of ascites and hydrops resolved completely after IUT and before delivery. Among the 18 fetuses with severe anemia, evidence of ascites/hydrops was present in 8 fetuses (44.4%).

Neonatal outcomes

The overall survival rate to discharge was 93.3%. Two mortalities were encountered, one secondary to proven late-onset sepsis and the other secondary to complications of congenital diaphragmatic hernia which was not detected antenatally and thought to be congenital heart disease. Neonatal mortality was not correlated with the severity of fetal anemia, presence of ascites and or hydrops, number of IUTs, GA at first IUT, GA at delivery, birth weight, or Hb at birth (P>0.05).

Delivery room: Cesarean section was the mode of delivery in 22 babies (73%). The median and mean gestational ages for planned delivery and unplanned delivery were 36 weeks and 35 weeks (range: 26-37 weeks), respectively. Vigorous resuscitation and respiratory support after delivery were required in 32% and 56.7% of cases, respectively. Unknown cause of fetal anemia, decreasing GA, low birth weight, and unplanned delivery were significantly associated with vigorous resuscitation (P<0.05) (Table 1).

Immediate post-birth: There was no significant correlation between low reticulocyte count at birth and the number of IUTs or the neonatal outcome variables, including late anemia, number of top-up transfusions, duration of admission, death, presence of Thrombocytopenia, Neutropenia, hepato- and/or splenomegaly, and cholestasis (P>0.05) (Table 2). The mean corpuscular volume at birth was lower than normal (mean of 81 fl). Baby blood group at birth was O negative in 21 cases (70%), mixed O negative with type A or B in 5 cases (16.7%), and baby's own blood group in 4 cases (13.3%). The mean time of blood group conversion in 14 babies was 70 days (range: 35-157 days).

Neonatal morbidity during hospitalization: All babies were admitted to the NICU with morbidities including respiratory, gastrointestinal, and hematologic problems (Table 3), either at delivery or later on during hospitalization. The most common morbidity was hyperbilirubinemia. Most of the neonates (93.3%) received phototherapy, 60% were given IVIG, and 7% required ET's.

The severity of fetal anemia was significantly correlated with the need for respiratory support and low reticulocyte levels at birth, with no significant differences in the other neonatal outcomes between the severe anemia and non-severe anemia groups (Table 4). A higher number of IUTs (>2) was only significantly correlated with the duration of admission and occurrences of hyporegenerative late anemia, but did

		Needed vigorous resuscitation					Needed respiratory support		
	Total	N (%)	P Value	OR	95%CI	N (%)	P value	OR	95% CI
Known cause of fetal anemia			<0.05	3.9	2.01, 7.3		>0.05	1.9	1.34, 2.77
Yes	27	7 (25.9)				14 (51.9)			
No	3	3 (100)				3 (100)			
Severity of fatal anemia			1	1	0.21, 4.7		<.05	5.2	1.06, 25.3
Mild-Moderate	12	4 (33.3)				4 (33.3)			
Severe	18	6 (33.3)				13 (72.2)			
GA at delivery			<0.05	8.5	1.45, 49.53		>.05	3.8	0.64, 23.05
<35 weeks	9	6 (66.7)				7 (77.8)			
>35 weeks	21	4 (19)				10 (47.6)			
Birth weight (kg)			>0.05	2.3	0.48, 11.1		>0.05	1.6	0.34, 7.2
<2.5	11	5 (45.5)				7 (63.6)			
≥ 2.5	19	5 (26.3)				10 (52.6)			
IUT number			>0.05	2.2	0.48, 11.1		>0.05	2.9	0.59, 14.72
≤ 2	11	5 (45.5)				8 (72.7)			
>2	19	5 (26.3)				9 (47.4)			
Mode of delivery			<0.05.	0.11	0.01, 0.61		>0.05	0.34	0.069, 1.68
Planned	19	3 (15.8)				9 (47.4)			
Unplanned	11	7 (63.6)				8 (72.7)			
Anemia (Hb<13 g/dl) at birth			>0.05	1.5	0.32, 7.5		>0.05	2.3	0.46, 11.69
Yes	10	4 (40)				7 (70)			
No	20	6 (30)				10 (50)			
Ascites/Hydrops			>0.05	2.3	0.49, 11.2		>0.05	1.57	0.34, 7.2
Yes	11	5 (45.5)				7 (63.6)			
No	19	5 (26.3)				10 (52.6)			
Spontaneous preterm labor			<0.05	0.18	0.03, 1.01		>0.05	0.33	0.055, 2.027
Yes	8	5 (62.5)				6 (75)			
No	22	5 (22.7)				11 (50)			
	OR: Odd Ratio; IVIG: Intravenous Immune Globulin; GA: Gestation Age; HB: Hemoglobin; IUT: Intrauterine Transfusion								

Table 1: Correlation between fetal and neonatal characteristics and the need for vigorous resuscitation and respiratory support after delivery.

Mode of delivery	
Planed, n (%)	19/(63.3)
Planned elective cesarean section	13 (43.3)
Planned induced vaginal delivery	6 (20)
Unplanned, n (%)	11 (36.7)
Spontaneous vaginal delivery	2 (6.7)
Urgent cesarean	9 (30)
Gestational age at birth (weeks)	
≤ 32 wk, n (%)	2 (6.7)
> 32-34 wk, n (%)	7 (23.3)
35-36 wk, n (%)	16 (53.3)
≥ 37 wk, n (%)	5 (16.7)
Condition at birth	
Neonates with shock at birth, n (%)	4 (14.3)
Neonates requiring intubation at birth, n (%)	3 (10.7)
Neonates requiring positive pressure ventilation at birth, n (%)	10 (32.3)
Median Apgar score at 1 min ± SD	8 ± 1.4
Median Apgar score at 5 min ± SD	9 ± 0.8
Number of babies with Apgar score less than 7 at 5 min, n (%)	1 (3.3)
Admission to the neonatal intensive care unit, n (%)	30 (100)
Median duration of neonatal intensive care unit (day)[range]	8 [2-68]
Lab value at birth	
Median hemoglobin level at birth (g/dL) ± SD	15 ± 2.9
Anemia at birth (Hb<13 g/dL), n (%)	10 (33.3)
Median bilirubin level at birth (mg/dL) ± SD	5 ± 2.3
Reticulocyte count at birth<1%, n (%)	18 (60)
Median of Mean corpuscular volume at birth*± S D	82 ± 13.1
Mean platelet count at birth ± SD	222 ± 82
Thrombocytopenia (platelet count<150), n (%)	7 (23.3)
Median duration of thrombocytopenia (day)	12
Neutropenia (neutrophil count<1500), n (%)	2 (6.7)
Mean Duration of Neutropenia (day) ± SD	16.8 ± 22.9
Median Duration of Neutropenia (day)range	2 (2-51)
Positive Direct Coombs test, n (%)	

Table 2: Delivery room outcomes and neonatal intensive care admission laboratory data for 30 baby.

not appear to be significantly correlated with the increased requirement of erythrocyte transfusions and other neonatal outcomes (Table 4) (P>0.05).

The presence of hepato- and/or splenomegaly at birth was significantly associated with an increased rate of cholestasis (P<0.05, CI 0.016, 1.02). Two out of six patients had very high Ferritin level at the time of diagnosis of cholestasis. However, there was no correlation between the occurrence of cholestasis and the number of IUTs (Table 4) (P=0.85, CI 0.126, 5.50).

Late anemia: Two-thirds of the patients developed late hyporegenerative anemia within a mean duration of 69 days. Top-up transfusion was required in 80% of babies until the Hb was normalized at 3 to 21 weeks of post-natal age. The first top-up transfusion was administered at a mean age of 19 days. Fifteen neonates received a second top-up transfusion. The average time between the first and second transfusion was 14 days. The use of IVIG was significantly correlated with a higher rate of top-up transfusions for late anemia and a longer duration of NICU admission (P<0.05) (Table 5).

Neurodevelopmental outcome at 12 months

Out of 28 discharged babies, 25 babies were followed until the age of 12 months. Three (12%) had abnormal neurodevelopment. Patient I developed spastic hemiplegic cerebral palsy and bilateral blindness due to Retinopathy of Prematurity (ROP), and MRI revealed periventricular leukomalacia. Patient II had bilateral blindness due to ROP with normal brain imaging. Patient III had delayed speech, and MRI showed callosum hypoplasia. These babies had severe fetal anemia and were born by urgent cesarean section due to spontaneous preterm labor or IUT complications at GAs of 26, 29, and 34 weeks, respectively. All needed active vigorous resuscitation at birth.

Discussion

Despite the proven role of anti-D prophylaxis in decreasing the incidence of hemolytic diseases, maternal Rhesus type D isoimmunization still occurs. The reported percentage of the Rh D-negative phenotype in Jordan was 12.8% [11]. The unfavorable fetal and neonatal outcomes that were observed in this study could have been avoided by implementing preventive measures including a good screening program for maternal blood group, red-blood-cell antibody identification at the time of admission, and administration of anti-D prophylaxis at the appropriate time.

This study reported a high rate of survival until discharge (93.3%) compared with those reported by Altunyurt et al. [4], Papantoniou et al. [12] and Weisz et al. [13] (73.5%, 83%_and 87%, respectively). This survival rate was not correlated with prenatal factors including the severity of fetal anemia, ascites, or hydrops; GA at first IUT; or GA at

Treatment modalities	
Number of neonates requiring exchange transfusion therapy#, n (%)	2 (6.7)
Number of neonates requiring phototherapy, n (%)	28(93.3)
Peak maximum total bilirubin, mg/dl	19
Number of neonates requiring IVIG, n (%)	18 (60)
Gastrointestinal morbidities	
Babies with gastrointestinal morbidities	
Number of neonates with direct hyperbilirubinemia (>20% of total bilirubin), n (%)	6 (20)
Mean duration of direct hyperbilirubinemia days (n=5) (range)	56.2 (2-225)
Spontaneous splenic tear after urgent unplanned cesarean section, n (%)	1 (3.3)
Number of neonates with hepatosplenomegaly at birth, n (%)	4 (13.3)
Number of neonates with isolated splenomegaly at birth, n (%)	1 (3.3)
Number of babies with persistent high liver enzyme levels at age 12 months* n (%)	2 (6.7)
Babies with respiratory morbidities	
Requiring ongoing respiratory support, n (%)**	17 (56.7)
Respiratory distress syndrome, n (%)	3 (10)
Transient tachypnea of newborn, n (%)	4 (13.3)
Pneumothorax, n (%)	1 (3.3)
Requiring oxygen support >1 day, n (%)	14 (46.7)
Chronic lung disease, (%)***	1 (3.3)
Myocardial dysfunction, n (%)	1 (8.3)
Mean duration of NICU admission, (range)	14 (2-68)
Retinopathy of prematurity Grade III or IV, n (%)	2 (6.7)
Periventricular leukomalacia, n (%)	1 (3.3)
Absent corpus callosum, n (%)	1 (3.3)
Death before discharge, n (%)	2 (6.7)

#had exchange transfusion in the first day of life
*Had high Ferritin level at birth (one had resolved high liver enzymes and the other had persistent high liver enzymes)
**The need for respiratory support was defined as the need for oxygen for more than 24 h via nasal cannula and/or continuous positive airway pressure and/or mechanical ventilation.
***Required oxygen at ≥ 36 weeks GA.

Table 3: Course of hospitalization and types of morbidities for 30 babies.

		Severity of fetal anemia					Number of IUTs				
		Severe	None severe				≤ 2	>2			
		n (%)	n (%)				n (%)	n (%)			
	Total		P Value		OR	95%CI		P value		OR	95%CI
Death				0.8	1.4	0.11, 17.09			0.9	0.85	0.068, 10.6
Yes	3	2 (66.7)	1 (33.3)				1 (33.3)	2 (66.7)			
No	27	16 (59.3)	11 (40.7)				10 (37)	17 (63)			
Appropriate for GA			0.8	0.72	0.059, 9.04			0.9	1.18	0.094, 14.67	
Yes	27	16 (59.3)	11 (40.7)				10 (37)	17 (63)			
No	3	2 (66.7)	1 (33.3)				1 (33.3)	2 (66.7)			
Duration of hospitalization				0.55	0.64	0.145, 2.78			0.034	0.162	0.027, 0.961
≤ 7 days	13	7 (53.8)	6 (46.2)				2 (15.4)	11 (84.6)			
> 7days	17	11 (64.7)	6 (35.3)				9 (52.9)	8 (47.1)			
Low reticulocyte count at birth (<1%)			0.015	7	1.36, 35.9			0.21	0.38	0.083, 1.78	
Yes	18	14 (77.8)	4 (22.2)				5 (27.8)	13 (72.2)			
No	12	4 (33.3)	8 (66.7)				6 (50)	6 (50)			
Thrombocytopenia			0.75	1.2	0.276, 5.87			0.45	1.8	0.39, 8.35	
Yes	11	7 (63.6)	4 (36.4)				5 (45.5)	6 (54.5)			
No	19	11 (57.9)	8 (42.1)				6 (31.6)	13 (68.4)			
Neutropenia				0.046	1.9	1.32, 2.80			0.39	0.37	0.036, 3.86
Yes	5	5 (100)	0				1 (20)	4 (80)			
No	25	13 (52)	12 (48)				10 (40)	15 (60)			
Cholestasis				0.57	0.6	0.099, 3.63			0.85	0.833	0.126, 5.50
Yes	6	3 (50)	3 (50)				2 (33.3)	4 (66.7)			
No	24	15 (62.5)	9 (37.5)				9 (27.5)	15 (62.5)			
Hepatomegaly and/or splenomegaly at birth			0.51	2.2	0.21, 24.08			0.6	0.53	0.049, 5.86	
Yes	4	3 (75)	1 (25)				1 (25)	3 (75)			
No	26	15 (57.7)	11 (42.3)				10 (38.5)	16 (61.5)			
Required vigorous resuscitation at birth				1	1	0.21, 4.71			0.284	2.33	0.48, 11.16
Yes	10	6 (60)	4 (40)				5 (50)	5 (50)			
No	20	12 (60)	8 (40)				6 (30)	14 (70)			
Required respiratory support				0.035	5.2	1.06, 25.3			0.17	2.9	0.59, 14.72
Yes	17	13 (76.5)	4 (23.5)				8 (47.1)	9 (52.9)			
No	13	5 (38.5)	8 (61.5)				3 (23.1)	10 (76.9)			
Hyporegenerative late anemia				0.4	1.9	0.39, 8.69			0.007	0.16	0.019, 0.611
Yes	20	13 (65)	7 (35)				4 (20)	16 (80)			
No	10	5 (60)	5 (60)				7 (70)	3 (30)			
Need for top-up transfusion				0.136	0.25	0.037, 1.66			0.08	4.85	0.71, 32.87
Yes	24	16 (66.7)	8 (33.3)				7 (29.2)	17 (70.8)			
No	6	2 (33.3)	4 (66.7)				4 (66.7)	2 (33.3)			
Delayed development*			0.25					0.53			
Yes	3	3 (100)	0				2 (66.7)	1 (33.3)			
No	25	14 (56)	11 (44)				8(32)	17 (68)			
*Odds ratio and 95% CI could not be calculated.											

Table 4: Correlation between the severity of fetal anemia and the number of intrauterine transfusions with neonatal outcome.

delivery; this result is consistent with the findings of Altunyurt et al. [4]. Possible explanations for the high survival rate in our study include the presence of good prognostic factors in the cohort [5,7,14], including initiation of treatment after 20 weeks of gestation, Rh D negative status as the most common cause of fetal anemia, and reversal of all cases of fetal hydrops or ascites with adequate IUT treatment.

Regarding the need for vigorous resuscitation at birth, this study's findings emphasize the importance of the anticipation of vigorous neonatal resuscitation in those babies with risk factors, including unplanned delivery due to IUT complications, spontaneous preterm labor leading to preterm delivery and a low-birth-weight neonate [15], fetal anemia of unknown cause, and the presence of associated exacerbating congenital abnormality (congenital diaphragmatic hernia in our case).

Our finding of no significant association between a low reticulocyte count at birth and the number of IUTs is consistent with the findings of Altunyurt et al. [4]. However, contrary to the previous studies conclusions [4,16,17], this study showed no association between a low reticulocyte count at birth and the need for top-up transfusions.

Our observed correlation between the severity of fetal anemia and the need for respiratory support can be explained by a delay in lung

		Baby received IVIG after birth			
	Total	IVIG, n (%)	No IVIG, n (%)	P value	95% CI
Required top-up transfusion				0.015	0.008, 838
No	6	1 (16.7)	5 (83.3)		
Yes	24	17 (70.8)	7 (29.2)		
Hyporegenerative late anemia				NS	
No	10	6 (60)	4 (40)		
Yes	20	12 (60)	8 (40)		
Required exchange transfusion				NS	
No	28	16 (57.1)	12 (42.9)		
Yes	2	2 (100)	0		
Duration of hospitalization				0.035	1.068, 25.309
≤ 7 days	13	5 (38.5)	8 (61.5)		
>7 days	17	13 (76.5)	4 (23.5)		

Table 5: Correlation between the use of IVIG during the neonatal period and the presence of adverse outcome.

maturity in patients with Rhesus type D isoimmunization, as described by Naeye [18]. However, Weisz et al. [13] reported no correlation between the severity of fetal anemia and the use of mechanical ventilation for respiratory distress syndrome [13].

In this study, only a small number of newborns required ET (6.8%); this is less than that reported by McGlone et al. [15] (20%), Weisz et al. [13] (47%) and Altunyurt et al. [4] (36%). Possible explanations include the implementation of the restrictive American Academy of Pediatrics criteria for ET in combination with the use of IVIG [10], the use of intensive phototherapy, the postponing of delivery to more than 35 weeks in two-thirds of the patients to allow for maturation of pulmonary and hepatic enzymes, and the frequent use of postnatal high-dose multiple IVIG in patients with Rhesus type D isoimmunization (60%).

The cause of late anemia has previously been explained by the presence of ongoing hemolysis [19], suppression of erythropoiesis [9,20], late anemia of hemolytic disease [21], and possibly the presence of anti-D antibodies in the bone marrow that destroy erythroid precursors [9]. In accord with the results of a previous study [22], hypo generative late anemia in our cohort was significantly correlated with the need for more than 2 IUTs. Several previous studies [23-25] have reported that the use of IVIG with alloimmunization decreases the duration of hospitalization, the need for ET, and the need for phototherapy However; other recent studies (high quality RCT) have shown that the use of IVIG has no effect on the rate of ET. The low rate of ET in this study is similar to recent studies without IVIG. There is no high-level evidence showing a clear benefit of IVIG [26,27].

This study shows that the use of multiple high doses of IVIG was significantly associated with an increased need for top-up transfusion for late anemia and with an increased duration of hospitalization ($P<0.05$). One possible explanation would be the presence of more severe disease in the group that received IVIG. However, in our study and some previous observations [27,28], IVIG was shown to have no positive effect on other neonatal outcomes. We would like to stress, however, that the use of high-dose IVIG was recently recommended to be used cautiously due to an increased incidence of NEC [29], which we did not note in our group of patients. This indicates the need to investigate the role of other alternative modalities, including intensive phototherapy, limited use of IVIG, and recombinant human erythropoietin [22]. The reported rate of Neurodevelopmental impairment is higher compared to a recent large cohort study [6].

This study was limited by several factors, including the small number of patients, the wide range of gestational age (26 weeks to term), the inclusion of 1 patient with congenital diaphragmatic hernia and the long-term follow-up in this series was incomplete as it did not include psychomotor assessments with standardized developmental tests (such as Bayley test, Griffith test or WISC or WIPPS etc). The true rate of Neurodevelopmental outcome might be higher than 12% after complete assessments. In addition, follow-up until age of 12 months is not long enough to determine with accuracy the long-term outcome. A longer time period is required at least until school age or at the very least 2 years or age. However, these results should provide useful information to health-care providers in planning the care of affected mothers and their babies.

Our findings emphasize the importance of the anticipation of vigorous resuscitation neonatal resuscitation in high-risk patients. Severe fetal anemia is associated with an increased need for respiratory support, and the need for more than 2 IUTs is significantly associated with the occurrence of hyporegenerative late anemia. Low reticulocyte count at birth is not associated with adverse postnatal effects. The use of multiple high-doses IVIG is significantly associated with an increased need for top-up transfusion for late anemia, with no positive effects on the other neonatal outcomes. It is important to implement preventive measures to decrease the risk of alloimmunization, including administration of anti-D prophylaxis at the appropriate time and a routine red-cell antibody screening program with each pregnancy.

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