Short Communication

Erika Hrastar*, Irena Bricl, Tanja Premru-Sršen, Jakob Gubenšek, Lilijana Kornhauser Cerar and Polona Pečlin

Successful management of severe hemolytic disease of the fetus and newborn (HDFN) due to anti-Kell

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Abstract

Objectives: Hemolytic disease of the fetus and newborn (HDFN) is a potentially life-threatening condition, caused by maternal alloimmune antibodies targeting fetal red blood cells. This report aims to present a case of severe early-onset anti-K-mediated HDFN, managed successfully with intravenous immunoglobulin (IVIG), therapeutic plasma exchange (TPE) and intrauterine transfusion (IUT), and to discuss comparable alternative approaches reported in the literature.
Methods: We treated a 32-year old woman in her third pregnancy with a high titer of anti-K alloantibodies (1:2048), detected in the first trimester. Weekly IVIG therapy of 1 g/kg was initiated at 15 weeks of gestation, followed by four TPEs and two IUTs. Due to suspected fetal anemia at 33 weeks of gestation, we opted for delivery. The newborn required phototherapy and erythropoietin treatment, with normal development at age two.
Results: To contextualize our approach, we reviewed published cases of anti-K-mediated HDFN and compiled a comparative table of treatment strategies and outcomes. Analysis showed that treatment protocols varied in IVIG dosing, TPE use, and timing, reflecting the absence of standardized approaches. These strategies were associated with delayed IUT and improved neonatal outcomes following prior fetal losses.
Conclusions: Our case, along with the review of published cases, supports the use of IVIG, with or without TPE, in managing anti-K alloimmunized pregnancies. The variability in treatment approaches underscores the need for individualized care based on maternal antibody titers, fetal antigen status, and disease progression, while emphasizing the importance of standardized protocols and prospective studies to guide optimal management.

Keywords: hemolytic disease; anti-K; intravenous immunoglobulin; therapeutic plasma exchange; intrauterine transfusion; breast milk

***Corresponding author: Erika Hrastar**, Research Assistant, Department for Diagnostic Services, Blood Transfusion Centre of Slovenia, Šlajmerjeva 6, 1000 Ljubljana, Slovenia, E-mail: erika.hrastar@ztm.si. https://orcid.org/0009-0003-5409-3863
Irena Bricl, Department for Diagnostic Services, Blood Transfusion Centre of Slovenia, Ljubljana, Slovenia
Tanja Premru-Sršen and Polona Pečlin, Division of Obstetrics and Gynaecology, Department of Perinatology, University Medical Centre Ljubljana, Ljubljana, Slovenia; and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
Jakob Gubenšek, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; and Department of Nephrology, University Medical Centre Ljubljana, Ljubljana, Slovenia
Lilijana Kornhauser Cerar, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; and Neonatal Intensive Care Unit, Division of Gynaecology and Obstetrics, Department of Perinatology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Introduction

Anti-K is found in the serum of about 1 per 1,000 pregnant women, however hemolytic disease of the fetus and newborn (HDFN) due to anti-K occurs in approximately 5% of Kell alloimmunized pregnancies [1, 2]. Without treatment, HDFN may result in progressive fetal anemia, fetal hydrops, asphyxia, and perinatal death [3].

Unlike other antibodies, anti-K alloantibodies not only induce hemolysis of fetal erythrocytes but also inhibit fetal erythropoiesis, leading to severe fetal anemia earlier in pregnancy. This creates a significant challenge, as intrauterine transfusion (IUT), the standard treatment for HDFN, carries increased risks when performed during early gestation [4, 5].

This communication aims to present a case of severe early-onset anti-K-mediated HDFN, managed successfully with intravenous immunoglobulin (IVIG), therapeutic plasma exchange (TPE) and IUT, and to discuss comparable alternative approaches reported in the literature.

Subjects and methods

We treated a 32-year-old woman, with no prior history of transfusion, who presented for the first antenatal visit in her third pregnancy at 8–9 weeks of gestation. The indirect antiglobulin test (IAT) was positive, identifying anti-K alloantibodies with a titer of 1:2048 (gel method). Her partner was phenotyped as K+k+.

Apart from a positive IAT, the pregnancy had been uneventful up to that point. A detailed history revealed that her first pregnancy in 2013 ended in a cesarean section due to cephalopelvic disproportion. Otherwise, the pregnancy was uneventful and the IAT was negative. Her second pregnancy in 2019 ended in miscarriage at 8 weeks of gestation, prior to the performance of antibody screening.

Clinical course and outcome

Considering the extremely high titer and antibody-dependent cell-mediated cytotoxicity of 25% (ADCC) of anti-K alloantibodies in early pregnancy (shown in Figure 1A), weekly IVIG therapy of 1 g/kg was initiated at 15 weeks of gestation. Antibody titers were monitored weekly and fetal anemia was assessed from 16 weeks onward using MCA-PSV (middle cerebral artery – peak systolic velocity) Doppler measurements (shown in Figure 1B). At 22 weeks of gestation, noninvasive prenatal testing (NIPT) confirmed the fetus to be K-positive.

An increase in anti-K titer and ADCC was observed at 24 weeks of gestation (shown in Figure 1A). In response, the IVIG dose was doubled, and four TPEs were performed, which resulted in the anti-K titer halving.

However, only a week after, at 25 weeks of gestation, during routine ultrasound monitoring of the MCA-PSV, severe fetal anemia was suspected, with the MCA-PSV MoM (multiples of median) exceeding 1.5 (shown in Figure 1B). Cordocentesis was performed, followed by an IUT of 40 mL blood, which resulted in an increase in fetal hemoglobin from 80 to 158 g/L.

At two subsequent points in the pregnancy, high MCA-PSV MoM indicated fetal anemia. Increased MCA-PSV MoM was detected at 30 weeks, prompting a second IUT of 35 mL of blood, which raised fetal hemoglobin from 105 g/L to 144 g/L. Only 3 weeks after the second IUT, again high MCA-PSV MoM (> 1.5) was measured, and anemia was suspected. After discussing options with the patient to perform IUT or deliver, a scheduled cesarean section was performed following a course of betamethasone for lung maturation.

A female neonate was delivered weighing 1,890 g, with a 5-min Apgar score of 9, cord hemoglobin of 116 g/L, and umbilical cord arterial pH of 7.32. After delivery, the newborn's Kell status was confirmed through genotyping. The direct antiglobulin test (DAT) was highly reactive with IgG antibodies, and anti-K was confirmed in the eluate. The newborn required phototherapy, while anemia remained stable with a hemoglobin level around 115 g/L. Pediatricians initiated erythropoietin treatment (Eprex® 250 IU/kg three times per week until 11 weeks of age) and discharged the infant with a hemoglobin level of 130 g/L, 21 days post-delivery. At 39 days, the infant was examined again at our center, with a hemoglobin of 115 g/L and hematocrit of 0.36. We also performed a heart ultrasound, which was normal. At the age of two, the child's development was evaluated as normal with a hemoglobin value of 132 g/L.

The follow up of the mother at six weeks postpartum revealed anti-K alongside anti-c and non-specific erythrocyte reactivity, most likely resulting from fetomaternal hemorrhage during delivery. This finding corresponds with the timing and Rh phenotype of the newborn (C+E-c+e+). The anti-K titer remained stable from the end of pregnancy, measured at 1:1024.

We also detected a relatively high titer of anti-K in maternal breast milk. We incubated maternal breast milk (colostrum) with K+ erythrocytes and performed a DAT on the erythrocytes. The test was reactive with IgG antibodies, and anti-K antibodies with a titer of 1:8 were confirmed in the eluate. This testing was repeated at three and six weeks postpartum, with consistent results. Although continued exposure to maternal antibodies through breast milk may contribute to delayed recovery from HDFN and persistent hemolysis, neonatologists decided that it was crucial for the infant to receive breast milk due to its high concentration of other protective immunological factors. As a result, breastfeeding was not discontinued [6].

Discussion

Anti-K alloimmunization presents unique challenges due to its dual mechanism: destruction of fetal erythrocytes and suppression of erythropoiesis [5]. Our case involved extreme maternal antibody reactivity early in gestation, with successful treatment using IVIG and TPEs to delay IUT.

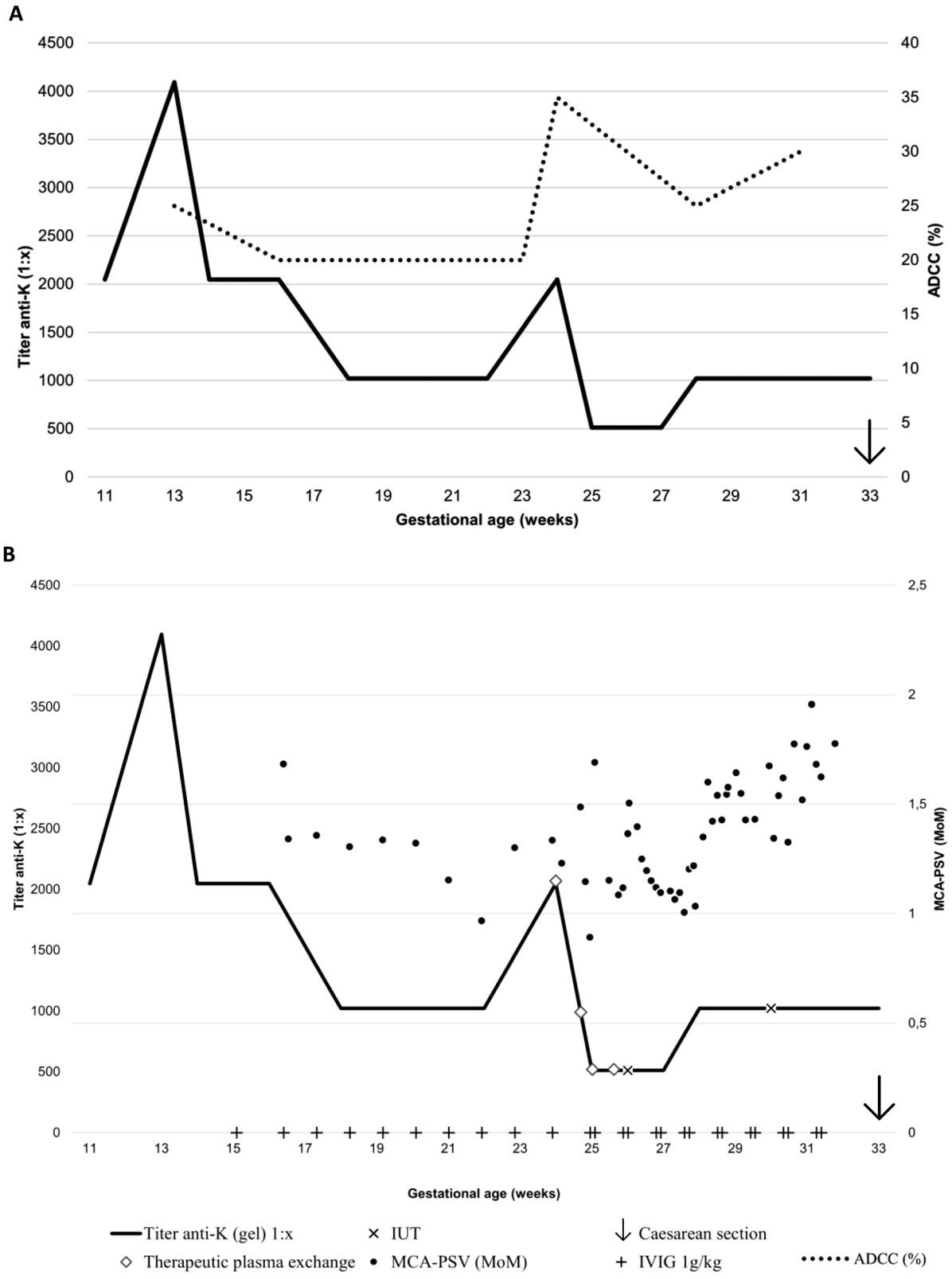

Figure 1: Immunologic activity and clinical management in anti-K alloimmunized pregnancy. (A) Anti-K and ADCC reactivity during pregnancy. (B) Treatment of the patient in response to the ratio of anti-K reactivity and MCA-PSV. ADCC, antibody-dependent cell-mediated cytotoxicity; IUT, intrauterine transfusion; TPE, therapeutic plasma exchange; MCA-PSV (MoM), middle cerebral artery-peak systolic velocity (multiples of median); IVIG, intravenous immunoglobulin.

IVIG and TPE are alternative therapies for managing severe early-onset red cell alloimmunization, particularly when IUT is not yet feasible. Both treatments, alone or in a combination, have shown potential in delaying disease progression and improving perinatal outcomes, though their use is based largely on case reports and small series [7].

The decision to use TPE or IVIG should be individualized in pregnancies at increased risk for severe HDFN. In the multicenter PETIT study by Zwiers et al. [8], IVIG was shown to delay the onset of severe fetal anemia and reduce the need for early intrauterine transfusion in pregnancies complicated by red cell alloimmunization, including both anti-D and anti-K antibodies. As IVIG transfer to the fetus is believed to begin around 12 weeks' gestation, this supports treatment schedules that commence in the late first trimester. When IVIG was initiated before 13 weeks' gestation, the incidence of fetal hydrops decreased from 24 to 4 %, and the need for neonatal exchange transfusion dropped from 37 to 9 %, highlighting the potential of early IVIG therapy to improve perinatal outcomes.

TPE alone may be insufficient due to rebound increases in maternal antibody levels following treatment, as discussed by Zwiers et al. in their review [9]. This rebound effect limits the long-term efficacy of TPE when used in isolation. To address this, a combined approach using IVIG and TPE has been proposed, showing promise in modulating the maternal immune response and improving outcomes in high-risk cases.

Although most data on anti-K alloimmunization stem from case reports, treatment protocols adapted mostly from anti-D management may offer useful guidance. One such regimen, described by Moise [10], includes three TPE sessions at 12 weeks' gestation, followed by an IVIG loading dose of 1 g/kg/day for two days and weekly infusions of 1 g/kg until 20 weeks. This protocol was subsequently applied by Ruma et al. [11], who used the same regimen in a cohort of nine patients, including two with anti-K antibodies. Similarly, Bellone and Boctor proposed a four-TPE protocol for anti-D alloimmunization. Their protocol began at 12 weeks, with two TPEs 48 h apart at 13 weeks and a final session at 14 weeks. IVIG was initiated after the third TPE and continued weekly until 28 weeks, allowing for improved IgG redistribution and stabilization of antibody titers [12]. Recommendations on monitoring and management of pregnancies affected by red cell alloimmunization were recently reinforced in a Delphi consensus. The panel supported IVIG initiation between 10 and 14 weeks at a dose of 1 g/kg/week (without a loading dose), specifically in pregnancies with prior fetal or neonatal death due to HDFN or a history of IUT before 24 weeks. Weekly MCA Doppler monitoring was recommended during IVIG therapy, and if signs of fetal anemia emerged, IVIG should be discontinued and IUT initiated. Notably, therapeutic plasma exchange (TPE) was not addressed in this consensus statement [13].

In our case, IVIG therapy was initiated early in pregnancy following confirmation of parental Kk status, indicating a potential risk for K-positive fetal antigen expression. TPE was deferred until non-invasive prenatal testing via cfDNA confirmed Kell-positive fetal status at 23 weeks' gestation. Given the procedural complexity and maternal risks associated with TPE, such as hemodynamic instability, infection, altered placental perfusion, electrolyte shifts, and reduced coagulation and immunoglobulin levels [9], its use should be reserved for cases with confirmed fetal antigen positivity. IVIG, supported by a favorable safety profile and increasing clinical evidence, may be considered earlier in gestation for pregnancies at elevated risk of severe HDFN. In this case, TPEs were performed primarily to lower the concentration of circulating antibodies and the IVIG dose was afterward doubled to prevent a rebound in antibody synthesis due to immunoglobulin depletion. Additionally, high doses of IVIG are thought to saturate the FcRn receptors, promoting increased catabolism of IgG [14, 15].

Our observation also adds to the limited literature on detectable anti-K antibodies in breast milk, confirming previous findings by Rasalam et al., and raising interesting considerations for neonatal immunohematology and breastfeeding guidance [16]. The persistence of low-titer anti-K reactivity in maternal colostrum – even weeks postpartum – warrants further research to understand its clinical relevance, although in our case, breastfeeding was safely continued.

In pregnancies complicated by anti-K alloimmunization, consistent patterns, such as delayed need for IUT, improved outcomes after multiple prior losses, and reduced incidence of fetal hydrops, support the consideration of IVIG, with or without TPE, despite the current evidence being limited and primarily retrospective. To support this, we compiled a comparative table summarizing similar cases, detailing variations in IVIG dosing, treatment protocols, use of IUT or TPE, and corresponding outcomes (Table 1). These cases reflect a wide range of clinical approaches, underscoring the absence of standardized protocols and the need for individualized treatment strategies based on disease severity and fetal antigen status.

Table 1: Treatment and outcomes of anti-K complicated pregnancies.

Case info	Clinical history	Immunologic profile	Interventions	Outcome
Lakhwani et al. 2011 [17]	G2, prior Kell alloimmunization (no HDFN), Tx history	Ab titer 1:256 Pat feno n/s Fet geno n/s	TPE start at 28 wk (4× every other day), then additional 10× between wk 29-33 IVIG not used First IUT at 27 wk Fet Hb at first IUT: 77 g/L No. IUTs: 1	Del at 34 wk, live birth, K+ newborn, Hb 116 g/L, DAT+, PTx, ET
Gallopi et al. 2023 [18]	G2, newly diagnosed anti-K and anti-C at 14 wk	Ab titer 1:64 (K), 1:1 (C) Pat feno Kk, cc Fet geno presumed K+, C+	TPE start at 19 wk (4×) IVIG from wk 20-28 IUT NR	Del at 37 wk (CS), live birth, Kk, Cc newborn, DAT+ (eluate: anti-K)
Bakhali et al. 2023 – Case 1 [19]	G4: 2nd pregnancy – AB at 8 wk; 3rd pregnancy – hydrops, anti-K, 2 IUTs, CS at 30 wk, Hb newborn 80 g/L, DAT+, 2 ET, PTx, died at 2 months due to heart failure	Ab titer 1:512 (→ 1:2048 before IVIG) Pat feno K+ Fet geno n/s	TPE start 17 wk (3×) IVIG from wk 19-24 First IUT at 24 wk Fet Hb at first IUT: 73 g/L No. IUTs: 4	Del at 34 wk (CS), live birth, K+ newborn, Hb 154 g/L, PTx
Fernández-Jiménez et al. 2001 – Case 2 [20]	G3: 2 IUFDs at 26 wk due to hydrops, anti-K, Tx history	Ab titer 1:512 Pat feno Kk Fet geno K+ (AC)	TPE start at 16 wk (4×), then at 18 wk (4×) and 3×/wk from wk 22 onward every 21 days until Del IVIG start at 16 wk (after each weekly TPE cycle) IUT NR	Del at 36 wk, live birth, K+ newborn, Hb 135 g/L, DAT weakly + (eluate: anti-K), IVIG
Vio et al. 2024 [21]	G2, newly diagnosed anti-K at 12 wk, no Tx history	Ab titer 1:1024 Pat feno Kk Fet geno K+ (cfDNA)	TPE start at wk 18 (15×) IVIG from wk 19 until Del IUT NR	Del at 34 wk (CS), live birth, K+ newborn, Hct 36 %, DAT+, PTx
Mayer et al. 2018 – Case 1 [22]	G2, newly diagnosed anti-K	Ab titer 1:1024 Pat feno KK Fet geno presumed K+	TPE not used IVIG from wk 14 to Del IUT NR	Del at 39 wk, live birth, Kk newborn, Hb 157 g/L, DAT+ (eluate: anti-K)
Nwogu et al. 2018 – Case 1 [23]	G4:1st pregnancy – placenta previa; 2nd pregnancy – IUFD at 21 wk due to suspected fetal anemia; 3rd pregnancy – AB at 5 wk; no Tx history, anti-K and anti-D	Ab titer 1:512 (K), 1:128 (D) Pat feno KK, Dd Fet geno K+, D+ (cfDNA)	TPE start at 10 wk (3×) IVIG start after TPE (loading dose 2 g/kg over 2 days, then 1 g/kg per wk for 10 wk) First IUT at 22 wk Fet Hct at first IUT: 20.3 % No. IUTs: 7	Del at 37 wk (CS), live birth, PTx
Nwogu et al. 2018 – Case 3 [23]	G6: 1st and 2nd pregnancy - uneventful; 3rd – anti-K, IUT at 18 wk, IUFD at 19 wk due to hydrops; 4th, 5th pregnancy – AB at 4–5 wk Anti-K and nonspec. IgG	Ab titer 1:1024 (K) Pat feno Kk Fet geno K+ (AC)	TPE start at 12 wk (3×) IVIG start after TPE (1 g/kg per wk for 11 wk) First IUT at 24 wk Fet Hct at first IUT: 26,8 % No. IUTs: 5	Del at 38 wk, live birth, therapy NR
Ruma et al. 2007 – Case 1 [11]	G2, neonatal death at 28 wk after 3 IUT	Ab titer 1:512 Pat feno n/s Fet geno K+	TPE start at 14 wk, 3× every other day IVIG start after TPE, duration n/s First IUT at 27 wk Fet Hct at first IUT: 27 % No. IUTs: 4	Del at 33 wk, live birth, therapy n/s

Table 1: (continued)

Case info	Clinical history	Immunologic profile	Interventions	Outcome
Ruma et al. 2007 – Case 3 [11]	G4, IUFD at 25 wk due to anti-K	Ab titer 1:256 Pat feno n/s Fet geno K+	TPE start at 13 wk, 3× every other day IVIG start after TPE, duration n/s First IUT at 24 wk Fet Hct at first IUT: 27 % No. IUTs: 5	Del at 3 wk, live birth, therapy n/s
Ruma et al. 2007 – Case 5 [11]	G4, IUFD at 19 wk due to anti-K	Ab titer 1:512 Pat feno n/s Fet geno K+	TPE start at 9 wk, 3× every other day IVIG start after TPE, duration n/s First IUT at 22 wk Fet Hct at first IUT 12 % No. IUTs 6	Del at 38 wk, live birth, therapy n/s
Ruma et al. 2007 – Case 9 [11]	G2, anti-K titer 1:8192, live birth at 37 wk, IUT NR	Ab titer 1:16,384 Pat feno n/s Fet geno K+	TPE start at 16 wk, 3× every other day IVIG start after TPE, duration n/s First IUT at 26 wk Fet Hct at first IUT 33 % No. IUTs 4	Del at 37 wk, live birth, therapy n/s
Patris et al. 2024 [24]	G3: 1st pregnancy – uneventful; 2nd pregnancy – fetal anasarca, oligohydramnios, fetal anemia, anti-K, 4 IUTs, termination at 32 wk cerebral damage, no Tx history	Ab titer n/s Pat feno KK Fet geno presumed K+	TPE not used IVIG start at 15 wk, weekly administrations First IUT at 28 wk Fet Hct at first IUT: 25 % No. IUTs: 2	Del at 33 wk (CS due to heart rate abnormalities), live birth, Hb 109 g/L, PTx
Vlachodimitropoulou et al. 2023 – Case 3 [25]	G8, IUFD at 24 wk after IUT, anti-K	Ab titer 1:512 Pat feno n/s Fet geno K+ (cfDNA or AC – n/s)	TPE not used IVIG from wk 11 until first IUT First IUT at 21 wk Fet Hb at first IUT: 84 g/L No. IUTs: 6	Del at 37 wk, live birth, therapy n/s
Vlachodimitropoulou et al. 2023 – Case 8 [25]	G5, IUFD at 19 wk due to anti-K	Ab titer 1:2048 Pat feno n/s Fet geno K+ (cfDNA or AC – n/s)	TPE not used IVIG from wk 13 until first IUT First IUT at 19 wk Fet Hb at first IUT: 81 g/L No. IUTs: 6	Del at 37 wk, live birth, therapy n/s
	G6, IUFD at 19 wk due to anti-K	Ab titer 1:512 Pat feno n/s Fet geno K+ (cfDNA or AC – n/s)	TPE not used IVIG from wk 14 until first IUT First IUT at 22 wk Fet Hb at first IUT: 82 g/L No. IUTs: 6	Del at 37 wk, live birth, therapy n/s
Hanson et al. 2024 [26]	G2, 1st pregnancy: uneventful; no Tx history	Ab titer 1:256 Pat feno K+ Fet geno Kk (uterine blood – during IUT)	TPE at 13 wk (3×) IVIG from wk 14 until Del First IUT 31 wk Fet Hb at first IUT: n/s No. IUTs: 2	Del at 36 wk (CS due to malposition), live birth, Hb 134 g/L, DAT+, therapy n/s

G, gravida; HDFN, hemolytic disease of the fetus and newborn; Tx, transfusion; Ab titer, antibody titer at enrollment; Pat feno, paternal fenotype; n/s, not specified; fet geno, fetal genotype; wk, week(s); TPE, therapeutic plasma exchange; IVIG, intravenous immunoglobulin; IUT, intrauterine transfusion; Fet, fetal; Hb, hemoglobin; No., number of; Del, delivery; DAT, direct antiglobulin test; PTx, phototherapy; ET, exchange transfusion; NR, not required; CS, cesarean section; AB, abortion; IUFD, intrauterine fetal demise; AC, amniocentesis; cfDNA, circulating free DNA; Hct, hematocrit.

Prospective trials are urgently needed to validate the efficacy of this therapeutic approach and to establish standardized treatment protocols for pregnancies at high risk of HDFN, such as those complicated by anti-K alloimmunization.

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