Case Report

Anti-U hemolytic disease of the fetus and newborn managed by multiple intrauterine transfusions: a case report and review of the literature

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Background: The U-antigen is part of the MNS blood group. Named for its almost universal expression, a U-negative phenotype is reported in ~1% of individuals of African descent. The spectrum of IgG-mediated anti-U hemolysis includes alloimmune disease of the fetus and newborn. The clinical presentation among affected newborns ranges from mild anemia to erythroblastosis fetalis.

Case Description: We present a case of maternal anti-U positivity and severe middle cerebral artery (MCA) Doppler concerning for anti-U hemolytic disease of the fetus and newborn managed by multiple intrauterine transfusions (IUTs). Uniquely, this case reports the lowest critical maternal anti-U titer to-date resulting in clinically significant fetal anemia. We also searched the literature using the general term "anti-U hemolytic disease" in PubMed to provide a review of case presentations, management methods, and outcomes. The maternal critical anti-U titer was initially 32 at 25 weeks and progressed to 64 by date of delivery. The initially normal fetus, at the 83rd growth percentile at 24 weeks, developed severe range MCA Doppler indices at 26 weeks [peak systolic velocity 59.9 cm/sec, 1.72 multiples of the median (MoM)]. The first percutaneous umbilical cord blood sampling (PUBS) at 265/7 weeks revealed a hemoglobin (Hgb) of 8.9 g/dL, 6.7% reticulocytes. IUTs were initiated for severe fetal anemia and predicted Hgb loss, four in total. Intrauterine growth restriction (<5%) developed by 36 weeks, prompting delivery by repeat cesarean section for non-reassuring fetal status. In conclusion, we successfully managed a case of severe anti-U-mediated fetal anemia by IUT performed via both fetal intravascular and intraperitoneal routes using donated U-negative blood. We identified 14 reports of anti-U hemolytic disease of the fetus and newborn that feature a broad range in clinical severity.

Conclusions: Anti-U hemolytic disease of the fetus and newborn is a rare, but potentially serious condition and should be managed in accordance with Rh alloimmunization guidelines. Antibody titers are inconsistently associated with clinical severity of disease. Surveillance with MCA Doppler and IUT with donated U-negative blood have shown promising outcomes.

Keywords: Case report; hemolytic disease of fetus and newborn; anti-U; intrauterine transfusion (IUT); percutaneous umbilical cord blood sampling (PUBS)

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Introduction

The U-antigen was first identified by Wiener *et al.* in 1953 following a fatal hemolytic transfusion reaction (1). In this and a subsequent report they observed near universal expression of the U antigen excepting ~1.2% U-negative subjects of African descent (1-4). Weiner *et al.* also identified an association between the MNS (formerly MN) blood group and the U-antigen, a finding further substantiated by Greenwalt and colleagues report that U-negative individuals did not react to anti-S or anti-s antibodies (2,3). As reviewed by Reid, the MNSs antigens comprise the second most complex blood antigen group following the Rh blood group (5). These antigens are located on two sialoproteins known as glycophorin A (GPA) and glycophorin B (GPB). The U-antigen is specific to GPB. The function of these proteins is to provide the glycocalyx of the red blood cell (RBC) an overall net negative charge to prevent adhesion to other RBCs, endothelium, and some organisms (5). As reviewed by Anstee, the absence or variance of GPA and GPB have been shown to confer resistance against malarial infection (6). The spectrum of IgG-mediated anti-U hemolysis includes alloimmune disease of the fetus and newborn. The clinical presentation among affected newborns ranges from mild anemia to erythroblastosis fetalis (7).

We present a case of severe fetal anemia requiring multiple intrauterine transfusions (IUTs) in the setting of maternal anti-U positivity. Uniquely, this case reports the lowest critical maternal anti-U titer to-date resulting in clinically significant fetal anemia. We also provide a review of available cases on anti-U hemolytic disease of the fetus and newborn. We present the following case in accordance with the CARE reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-72/rc) (8).

Case presentation

Our patient's mother was a 30-year-old female, Gravida 5 Para 2, A+, anti-U positive (1:8), with chronic iron deficiency anemia and obesity (BMI 41). Her obstetric history was: G1—term birth by spontaneous vaginal delivery, G2—spontaneous abortion, G3—term cesarean section for arrest of dilation, and G4—twin fetal demise in context of acute intraamniotic infection at 20+ weeks gestation, chronic placental abruption, anhydramnios, and anti-U antibody (1:16) identified during workup. A complete erythrocyte antigen profile obtained during her fourth pregnancy when she was found to be anti-U positive

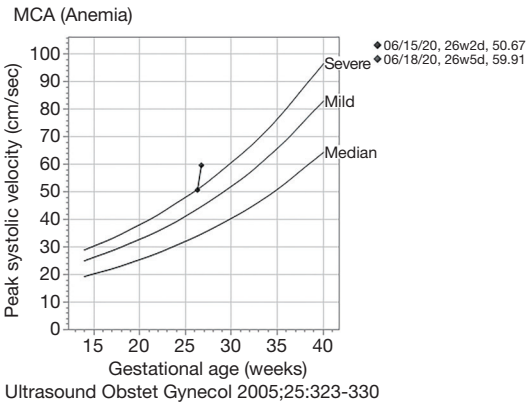

Figure 1 MCA peak systolic velocity digitally plotted against a nomogram stratified by severity. MCA, middle cerebral artery.

showed: blood type A, Rh (D+, c+, C–, E–, c+), FY (a–, b–), JK (a+, b–), KEL (k+), LE (a–, b+), and MNS (M–, N+, U–, s–). Antibody titers during the reported pregnancy were 8 at 8 weeks gestation, 32 at $25^{1/7}$ weeks gestation and 64 at $26^{4/7}$ weeks gestation. Additional antibody testing performed at four different time points during the prenatal period screened against antigens: B, C, c, E, e, F, C^{w}, V, K, k, Kpa, Kp^{b}, JS^{a}, JS^{b}, Fy^{a}, Fy^{b}, JK^{a}, JK^{b}, Xg^{a}, LE^{a}, LE^{b}, S, s, M, N, P1, LU^{a}, and LU^{b} antibodies. Only anti-U was positive at each screen. In the currently reported pregnancy, prenatal screening labs indicated: rubella immunity and no hepatitis B virus, hepatitis C virus, gonorrhea, chlamydia, syphilis, or human immunodeficiency virus (HIV) infection.

She was found to be pregnant with our patient at approximately 8 weeks gestation. The first ultrasound performed at 24+ weeks showed appropriate fetal growth at the 83rd percentile. At $25^{1/7}$ weeks, she had a critical anti-U titer of 32 and weekly fetal middle cerebral artery (MCA) Doppler were initiated to screen for fetal anemia. At $26^{2/7}$ weeks, MCA Doppler indices were at the severe range at 50.67 cm/sec [1.49 multiples of the median (MoM)] without fetal hydrops. A repeat MCA Doppler was performed at $26^{5/7}$ with a peak systolic velocity of 59.91 cm/sec (1.72 MoM). We defined fetal anemia based on values defined by Nicolaides *et al.* and plotted in *Figure 1* (9). Percutaneous umbilical cord blood sampling (PUBS) was performed to assess the degree of anemia and IUT with fresh blood [fresh, cross-matched, leukocyte depleted, cytomegalovirus (CMV) negative, irradiated, high hematocrit (Hct)] was planned if severe anemia was confirmed.

(I) PUBS performed at $26^{5/7}$ weeks demonstrated a pre-transfusion peripheral blood count with

a fetal Hgb of 8.9 g/dL and a reticulocytosis of 6.7%, documenting severe fetal anemia and an intraoperative point-of-care (HemoCue) hemoglobin (Hgb) of 11.1 (range, 10.9–11.3) g/dL. Based on the data from Nicolaides *et al.* the <2 SD cutoff for 26 weeks is 10.8 g/dL and for 27 weeks is 11.0 g/dL (9). With such close proximity to these cutoffs and a highly abnormal MCA Doppler we opted to pursue transfusion. Therefore, 40 mL of packed red cells were transfused intravascularly (donor Hgb 19.5 g/dL) with the expectation to raise fetal Hgb to 15 g/dL. However, a post-transfusion Hgb was not obtainable.

(II) At $28^{3/7}$ weeks, due to difficulty obtaining fetal intravascular access, a pre-transfusion fetal Hgb was not obtained and transfusion of 80 mL of packed red cells (donor Hgb 21.5) was given via the intraperitoneal route.

(III) At $31^{3/7}$ weeks PUBS demonstrated a fetal pre-transfusion Hgb 12.4 g/dL. Similar to PUBS #1, given the proximity of this Hgb to the 31-week cutoff of 11.8 g/dL, documented severe fetal anemia on the prior PUBS, and difficulty in obtaining intravascular access, we transfused 30 mL of packed red cells (donor Hgb 20.3) intravascularly raising the post-transfusion Hgb to 14.6 g/dL.

(IV) At $35^{3/7}$ weeks PUBS demonstrated a pre-transfusion fetal Hgb of 12.9 g/dL. By extrapolation, the 35-week cutoff is 12.6 g/dL. Using the same reasoning as prior PUBS, 45 mL of packed red cells (donor Hgb 22) were transfused intravascularly. The post-transfusion Hgb was 14.6 g/dL.

Intrauterine growth restriction was noted on ultrasound 1 day after the last IUT with an estimated fetal weight of 2,189 g (<5%) prompting delivery by repeat cesarean section at 36 weeks with Apgar of 8 and 9. Maternal anti-U titer at this time was found to be 64. Birthweight was 2,205 g, small for gestational age, and physical exam and vital signs were unremarkable with no tachycardia, pallor, or jaundice. Pertinent blood work obtained at 20 minutes of life were: Hgb 16.0 g/dL, reticulocyte 5.6%, blood type A+, direct antiglobulin test 3+, total serum bilirubin 2.5 mg/dL, and direct bilirubin 0.5 mg/dL. The patient fed ad lib and was stable in room air. Early prophylactic phototherapy was initiated and discontinued by 64 hours of age. The patient was discharged home at ~110 hours of life. The discharge Hgb was 16.7 g/dL, Hct 50%, reticulocyte 4.2%, total serum bilirubin of 6.0 mg/dL and direct bilirubin of 0.6 mg/dL. She did not evidence late onset anemia requiring blood transfusion. At 2-month follow-up, the patient was developmentally appropriate. *Figure 2* visually depicts the patient's prenatal and postnatal course.

Please note that all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's mother for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We report a case of severe anti-U-mediated fetal anemia successfully managed by IUT. IUT was performed via both fetal intravascular and intraperitoneal routes using donated U-negative blood. The maternal critical anti-U titer of 64 in our case was lower than those previously reported among IUT-managed cases (8,000, 512, and 256) (10-12). Nevertheless, fetal Hgb levels ranging from 8.9 g/dL at 26 weeks to 12.9 g/dL at 35 weeks characterized the in-utero course. The first IUT was based on the abnormal MCA Doppler being consistently in the severe-anemia range. Subsequent procedures were time-driven based on the predicted rate of donor RBC loss. The decision to transfuse was based on fetal pre-transfusion Hgb but also on the difficulty in both securing fetal intravascular access and in obtaining U-negative blood for both fetus and mother (9).

Postnatally, the infant evidenced a 3+ positive direct antiglobulin test with anti-U eluted from the newborn RBCs. The postnatal course was relatively benign. Our infant, similar to one other IUT case, was managed with phototherapy alone and did not need RBC transfusion during the birth hospitalization or as an outpatient in follow-up (12). In contrast, one other IUT neonate required phototherapy, an exchange transfusion, and three blood transfusions postnatally, while another required phototherapy and a blood transfusion for symptomatic anemia (10,11).

We searched the literature using the general term "anti-U hemolytic disease" in PubMed and identified 14 reports, in English, featuring hemolytic disease of the fetus and newborn (*Table 1*). Three non-English articles were not included in our review (24-26). The table highlights the potential for severe fetal/neonatal involvement in anti-U hemolytic disease: 4 of the 20 cases

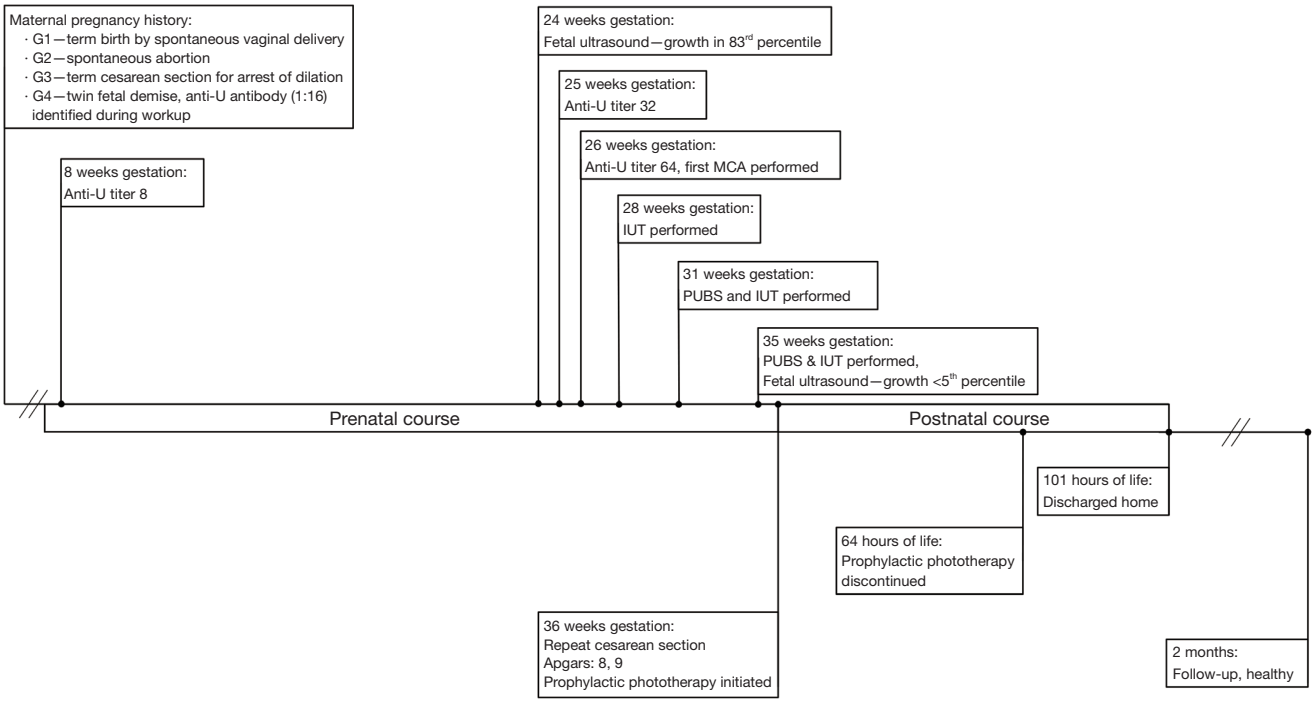

Figure 2 A timeline depiction of the patient's prenatal and postnatal course. MCA, middle cerebral artery; IUT, intrauterine transfusion; PUBS, percutaneous umbilical cord blood sampling.

merited IUT (including ours), there was one intrauterine fetal demise (IUFD) secondary to erythroblastosis fetalis, and 3 infants who did not undergo IUT required postnatal double volume exchange transfusion (10-16). These cases were characterized by maternal anti-U titers in the 64 to 8,000 range (10,15). The wide range of maternal antibody titers suggest this metric is not a strong predictor of the clinical course of the fetus or newborn. Severe cases resulting in fetal anemia were seen at maternal anti-U titers as low as 64 (15). High titers do not necessarily predict a severe fetal or neonatal course; in three pregnancies with maternal anti-U titers of 4,000 the fetus was unaffected and the newborn was managed with phototherapy alone with no need for postnatal transfusion (10). Only titers below 32 generally resulted in a benign postnatal course of mild jaundice and phototherapy, a conclusion shared by Rana *et al.* (17). Nevertheless, if anti-U antibody is present, antibody titers should be followed throughout pregnancy and close fetal monitoring is warranted when a critical titer is observed. As reviewed by Adam and Lombaard in 2016, intrapartum management of anti-U hemolytic disease should be in accordance with the management of Rh alloimmunization (12).

Conclusions

Anti-U hemolytic disease of the fetus and newborn is a rare, but potentially serious condition and should be managed in accordance with Rh alloimmunization guidelines. Antibody titers are inconsistently associated with clinical severity of disease. Surveillance with MCA Doppler and IUT with donated U-negative blood have shown promising outcomes.

Table 1 Summary of cases of anti-U hemolytic disease of the fetus and newborn (10-23)

Year	Pregnancy[#]	Maternal ancestry***	MBT	Maternal antibody titer	Infant DAT	Fetal/neonatal course
1961, (18)	G6	Black	B+	Anti-U: 32	Positive: anti-U	Uncomplicated, no treatment
1964, (13)	G4	Black	O+	Anti-U: 640	Not obtainable	IUFD at 36 weeks gestation
				Anti-N: 16		Postmortem: fetal hydrops secondary to erythroblastosis fetalis
1976, (14)	G4	Black	–	Anti-U: 128 (8 weeks) → 1,024 (30 weeks)	Positive: anti-U	Phototherapy
						Double volume exchange transfusion
1981, (15)	G7	Black	B–	Anti-U 64	Positive anti-U and anti-D	Double volume exchange transfusion
				Anti-D 256		
1981, (16)	G7	Nigerian	O+	Anti-U: 512	Positive: anti-U	Phototherapy
						Double volume exchange transfusion
1982, (19)	G1	Jamaican	O+	Anti-U first detected at 16 weeks → 4 (34 weeks)	Positive (no eluate reported)	Phototherapy
1983, (20)	G2	Black	–	Negative at 15 weeks → anti-U: 32 (at delivery)	Positive: anti-U	Uncomplicated, no treatment
	G3			Anti-U 16	Positive: anti-U	Uncomplicated, no treatment
1984, (21)	G2	Black	AB+	Positive (no titer reported)	Positive: anti-U	Uncomplicated, no treatment
1998, (10)	G3	Nigerian		Anti-U: 4	Negative	Phototherapy
	G4			Anti-U: 16 (7 weeks) → 4,000 (38 weeks)	Positive (no eluate reported)	Phototherapy
	G3	Zimbabwean	–	Anti-U: 16 (19 weeks) → 128 (29 weeks) → 256 (30 weeks) → 4,000 (35 weeks)	Positive (no eluate reported)	Phototherapy
	G4			Anti-U: 512 (23 weeks) → 2,000 (37 weeks)	Positive (no eluate reported)	Phototherapy
	G2	Ghanaian	–	Negative (11 weeks) → anti-U: 8,000 (33 weeks)	Positive (no eluate reported)	Phototherapy
						Six postnatal blood transfusions
	G3			Anti-U: 1,000 (20 weeks) → 8,000 (32 weeks)	Positive (no eluate reported)	IUT ×4
						Phototherapy
						Double volume exchange transfusion
						Three postnatal blood transfusions

Table 1 (*continued*)

Table 1 (*continued*)

Year	Pregnancy[#]	Maternal ancestry***	MBT	Maternal antibody titer	Infant DAT	Fetal/neonatal course
1999, (22)	G2	Black	A+	Anti-U: 4 (18 weeks) → 8 (24 weeks) → 16 (34 weeks)	Positive: anti-U	Uncomplicated, no treatment
2003, (23)	G4	Brazilian**	–	Anti-U: 32	Positive: anti-U	Phototherapy
2011, (17)	G4	Nigerian	–	Anti-U: 4 (16 weeks) → 8 (28 weeks) → 32 (36 weeks) → 256 (37 weeks)	Positive (no eluate reported)	Phototherapy
2013, (11)	G4	Somalian	A+	Anti U: 256 (15 weeks)	Positive: anti-U	IUT ×4 Phototherapy One postnatal blood transfusion
2016, (12)	G1	Black	O–	Anti-U: 512 (25 weeks) Anti-D: not detected	Positive: anti-U	IUT ×2 Uncomplicated postnatal course, no treatment
2020*	G5	Black	A+	8 (8 weeks) → 32 (25 weeks) → 64 (26 weeks)	Positive: anti-U	IUT ×4 Phototherapy

*, current case report. **, in this reference from Brazil, mother is identified as "brown". This term is often used in Brazil for individuals of admixed European, West African, and Amerindian descent. ***, when specified, an individual's country of origin was used for maternal ancestry. However, some studies pre-dating the 2000s used derogatory and pejorative rhetoric when describing a patient's ancestry, race, or ethnicity. As such, the term Black is broadly used to convey ancestry by way of referring to a shared history, identity, or community which includes individuals within Africa or part of the African diaspora. G, gravida; MBT, maternal blood type; DAT, direct antiglobulin test; GA, gestational age; IUT, intrauterine transfusion; IUFD, intrauterine fetal demise.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-21-72/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-72/coif). JFW reports serving as a consultant in medicolegal cases associated with kernicterus. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's mother for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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