Autologous intrauterine transfusion in a case of anti-U

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Abstract

BACKGROUND: Minor red blood cell antibodies are becoming a more common cause of hemolytic disease of the newborn. Anti-U are a rare alloantibody found almost exclusively in people of black descent. There is limited experience to guide the management of pregnancies complicated by anti-U. Furthermore, there is often no suitable cross-matched blood available for transfusion of a patient with anti-U.

CASE REPORT: A 21-year-old P0G1 presented at 25 weeks' gestation with D– disease in pregnancy. She had a significant indirect antiglobulin test titer of 512. Anti-U were identified and no suitable cross-matched blood was available. Maternal blood was prepared for autologous intrauterine fetal transfusion. Two such transfusions were performed.

RESULTS: A healthy fetus delivered at 32 weeks that did not require phototherapy or an exchange transfusion.

CONCLUSION: Autologous transfusion of prepared maternal blood provides a safe option for intrauterine fetal therapy in pregnancies complicated by rare alloantibodies.

ABBREVIATION
MCA-PSV - middle cerebral artery peak systolic velocity

Hemolytic disease of the newborn (HDN) was a significant cause of fetal morbidity and mortality until the introduction of amniocentesis, intrauterine transfusion, controlled early delivery, and exchange transfusion in the management of severe alloimmunized women and their fetuses. The universal use of RhIG has reduced the prevalence of HDN, but has brought the minor red blood cell (RBC) antibodies to the fore.

A 21-year-old P0G1 was referred to the fetal unit for evaluation at 25 weeks' gestation. She was blood group O, D–, indirect antiglobulin test (IAT) reaction positive with a significant titer of 512. This was her first pregnancy and she had had no prior blood transfusions. Thus far the pregnancy was uncomplicated.
On fetal assessment she was 25 weeks 4 days pregnant with an estimated fetal weight of 774 g. The fetus was appropriately grown for gestation with normal amniotic fluid index and umbilical artery Doppler. The fetus appeared structurally normal and there was no evidence of hydrops fetalis. The middle cerebral artery peak systolic velocity (MCA-PSV) was normal.

One week later (26 weeks 4 days) the MCA-PSV V-Max (56.6 cm/sec) was greater than 1.5 multiples of median, indicating a fetal anemia. The patient was counseled and an intrauterine transfusion was planned. At the time of the transfusion, the blood services (SANBS) informed us that the patient had anti-U, from the MNS antigen system, as determined by an 11-reagent panel. At that time no suitable blood was available for the transfusion. The procedure was abandoned and corticosteroids were administered for fetal lung maturity.

After consultation with a hematologist and further discussion with the patient, the option of autologous transfusion of maternal blood was considered. The patient’s hemoglobin (Hb) level was 11.7 g/dL. The patient donated 85 mL of blood which was then leukoreduced, irradiated, and tightly packed to a hematocrit (Hct) of 75%. We obtained 25 mL of blood, which was transfused uneventfully into the umbilical vein, at 28 weeks’ gestation. The fetal Hb level was 8.7 g/dL before transfusion. The fetal direct antiglobulin test (DAT) reaction was positive. We were unable to determine the antibody status as we had a limited fetal blood sample. The patient received 600 mg of intravenous iron (Venofer) in three divided doses over the course of a week.

At follow-up 1 week later the MCA-PSV V-Max (56 cm/sec) was again elevated. The mother donated an additional 100 mL of blood, which was prepared. Her Hb level at this time was 11.1 g/dL. A second intrauterine fetal transfusion of 38 mL of prepared maternal blood was carried out uneventfully at 30 weeks 3 days' gestation. The fetal Hb level was 10.8 g/dL before transfusion. We did not retest the DAT as we were unable to obtain adequate amount of fetal blood at this procedure. At this time the fetus was appropriately grown with an estimated fetal weight of 1565 g, with a normal amniotic fluid index and umbilical artery Doppler. There was no evidence of hydrops fetalis.

At the 32-week follow-up visit the fetus weight was 1770 g, which was appropriate. However, the umbilical artery Doppler was raised (0.84) and the amniotic fluid index was 19.8 cm. The MCA-PSV Vmax was also increased (56.6 cm/sec), although less reliable after two intrauterine fetal transfusions. The neonatologist was consulted and it was decided to rather deliver the fetus than repeat an autologous transfusion. A healthy 1.8-kg neonate with an Apgar score of 7 of 10 and 9 of 10 at 1 and 5 minutes, respectively, was delivered via Cesarean section. The maternal Hb level was 11 g/dL. The neonatal Hb level was 13 g/dL and he did not require phototherapy or exchange transfusion. The neonate was blood group O, D+, U+. The neonatal DAT was weakly positive but the IAT reaction was positive, indicating maternal antibodies. Anti-U were identified in neonatal blood as determined by an 11-reagent panel. We thus postulated that the anemia was due to anti-U. We have no further follow-up information on the child as the family moved away from the area.
DISCUSSION

Development of hemolytic disease of the newborn requires maternal exposure to an RBC antigen not expressed on maternal RBCs and the generation of an alloantibody. Sources of exposure include previous blood transfusion to the mother, fetomaternal bleeding, or shared needles. The likelihood of alloimmunization increases with greater volumes of allogeneic blood to which the woman is exposed. Exposure to as little as 0.5 mL of allogeneic blood can cause sensitization.\[1\]

Sensitization to minor RBC antigens may be more likely as routine testing of donor blood for antigens other than ABO and D is not performed. After maternal sensitization to an RBC antigen through any of the above mechanisms, subsequent exposure during a future pregnancy will elicit an antibody response of variable intensity and timing. To cause hemolysis of fetal cells, the maternal alloantibody must be transported across the placenta; thus antibodies of the IgG class are usually implicated.\[1\]

Minor RBC antibodies are immunoglobulins associated with RBC antigens other than ABO and D. They usually develop in response to exposure to foreign RBC antigens, but may occur naturally from exposure to bacteria or viruses. Minor antibodies associated with HDN are the Kell group, Duffy, MNS system, and P system. The MNS system contains the M, N, S, s, and U antigens, as well as 32 other rare antigens. Naturally occurring antibodies to M and N are seen in a small percentage of the general population in the absence of exposure to allogeneic blood. Mild to severe anemia has been associated with anti-U. Smith and colleagues\[2\] recommended that an anti-U titer of 128 or greater or gestational age greater than 17 weeks is an indication for assessment of hemolysis in the fetus. Less than 1% of the black population is U–.\[3\] However, anti-U, a rare cell alloantibody occurs exclusively in people of black descent.\[2\] All except one case report in the literature occurred in black patients (see Table 1).

There is limited experience on which to base management of pregnancies complicated by minor RBC antibodies. The American College of Obstetrics and Gynecology\[7\] advises that care of these women should be the same as that of women with Rh alloimmunization. Doppler assessment of the fetal MCA-PSV is the best method for monitoring fetuses at high risk of anemia.\[8\] This is based on the premise that the anemic fetus preserves oxygen delivery to the brain by increasing cerebral flow of low viscosity blood. The sensitivity of increased MCA-PSV above 1.5 multiples of median has approximately 100% sensitivity in the prediction of moderate to severe anemia.

The infusion of RBCs into the fetus is one of the most successful in utero therapies. It is indicated to prevent fetal death due to severe anemia and is performed between 18 and 35 weeks’ gestation. Usually group O D– blood is transfused. Donor units are screened for cytomegalovirus, gamma irradiated to prevent graft-versus-host reaction, leukoreduced, washed, and tightly packed to a Hct level of 75% to 85%.

Autologous donation by pregnant women can be considered, especially when rare antibodies are present. The advantage of this is that this eliminates the mother’s risk of becoming sensitized to donor RBC antigens. However, the mother should ideally have a Hb
<table>
<thead>
<tr>
<th>Country</th>
<th>Pregnancy details</th>
<th>Pregnancy outcome</th>
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| Brazil² (nonblack patient) | P3G4  
No prenatal data  
Sickle cell anemia, prior transfusions  
Antenatal antiglobulin test negative  
Mother found to have anti-U after delivery | Neonate born at 38 weeks with good Apgar score  
Neonate had anti-U  
Required phototherapy |
| Niger⁴        | P0M1G2  
Antenatal anemia, prior transfusions  
Antenatal antiglobulin test negative | Neonate antiglobulin test negative |
| United States⁶ | P1G2  
Anti-U detected antenatally | Neonate born at 38 weeks  
Neonate had anti-U  
No phototherapy required |
| Nigeria⁶      | P3G4  
Anti-U titer increased from 4 to 256 at term  
No fetal anemia detected antenatally | Neonate born at 38 weeks  
Neonate had anti-U  
Required phototherapy |
| Nigeria²      | P0M1G2  
Anti-U titer increased from 4 to 4000 at term  
No fetal anemia detected antenatally | Required phototherapy |
| Zimbabwe²     | P0M1G2  
Anti-U detected  
P1M1G3  
Anti-U titer increased from 16 to 4000  
P2M1G4  
Anti-U titer increased from 512 to 2000 | No phototherapy required |
| Ghana²        | P0M1G2  
Sickle cell trait  
Anti-U titer 8000 | Growth-restricted neonate delivered at 32 weeks with good Apgar score  
Sickle cell negative  
Neonate had anti-U  
Required phototherapy |
|              | P1M1G3  
Sickle cell trait  
Anti-U titer increased from 1000 to 8000  
Antenatal anemia detected: received four intrauterine transfusions | Neonate born at 32 weeks due to fetal bradycardia during fourth intrauterine transfusion  
Neonate required phototherapy and an exchange transfusion |
level of more than 12 g/dL. A potential fetal advantage is that the RBCs may have a longer half-life and thus decrease the number of total intrauterine transfusions required.[9]

The management of pregnant women with rare antibodies in the absence of appropriately cross-matched blood products poses a challenge. The use of maternal donation for intrauterine transfusion offers an alternative for this potentially life-saving procedure. The use of maternal RBCs for intrauterine transfusions has been successfully described in cases with anti-K(u),[10] anti-Jsb,[11] and anti-Rh17.[12] The largest series of maternal blood donations during pregnancy was described by Gonsoulin and colleagues.[13] A total of 21 alloimmunized pregnant women donated a total of 77 units of blood for intrauterine transfusions. There was one fetal and two neonatal deaths. No maternal or fetal adverse events were attributed to the intrauterine transfusions in this series.

Another study compared the use of maternal blood versus donor blood for intrauterine transfusions. It was observed that the decline in fetal Hct was much slower in those fetuses receiving maternal blood. Furthermore, neonates who have received maternal blood required fewer postnatal transfusions.[14]

The maternal–fetal ABO-mismatched incompatibility is not deemed to present a significant risk for intrauterine transfusion because anti-A and anti-B are not detected in a large population of fetuses during gestation and are absent or only weakly detectable in cord serum. However, ABO-mismatched transfusion should only be reserved for rare instances when antigen-compatible group O blood is unobtainable.[12]

Pregnant women who donate blood should receive iron supplementation. Erythropoietin (EPO) can also be considered to increase maternal Hct, if necessary. Case reports of EPO use later in pregnancy have reported no adverse events.[15]

Intrauterine fetal transfusion is not without risk.[16] These risks include perinatal death, emergency Cesarean section, infection, premature rupture of membranes, inadvertent arterial puncture, fetal tachycardia or bradycardia, or bleeding from the puncture site.

Overall survival after intrauterine transfusion is 89% but varies by center, experience, and presence of hydrops fetalis. Survival is worse if hydrops is present or severe anemia occurs before 20 weeks’ gestation. Available data on long-term outcome of the child are necessary. The Lotus study[16] assessed the risk factors and incidence of neurodevelopmental impairment in children with HDN treated with intrauterine transfusion. They found that the neurodevelopmental outcome for children compared favorably with a group of high-risk, very-low-birthweight infants (10% vs. 18%) but less favorably with a healthy control group (10% vs. 6%). Fetal hydrops was found to be associated with increased mortality. Not much is known regarding the severity of fetal anemia and long-term neurodevelopmental outcome. In conclusion, autologous transfusion provides a safe option for intrauterine therapy in pregnancies complicated by rare alloantibodies.

**CONFLICT OF INTEREST**

The authors have disclosed no conflicts of interest.
REFERENCES


