Severe hydrops in Rh(D) positive mother due to antenatally diagnosed anti–c antibodies: First case report from India.

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Abstract:

Introduction: Rh hemolytic disease of newborn is the prototype of maternal isoimmunisation and fetal hemolytic disease. There are other minor blood group antigens capable of causing alloimmunisation and hemolytic disease such as c, C, E, Kell and Duffy. In India, after confirmation of blood group, antibodies are screened only in Rh (D) negative mothers with Rh (D) positive husband. Hydrops in Rh positive woman are investigated on lines of non immune hydrops.

Case presentation: Here we report first case from India where irregular antibodies were requested in O positive mother to investigate fetal hydrops. Anti- c was revealed and fetus was treated with compatible O negative, c negative intrauterine blood transfusion successfully. Postnatally baby was treated with double volume exchange transfusion with same compatible blood and discharged on Day 30 of life.

Conclusion: This highlights importance of screening women for irregular antibodies in bad obstetric history and fetal hydrops. This will assist in proper diagnosis and treatment of fetus with appropriate antigen negative cross matched compatible blood for successful outcome. Anti-c immunoglobulin is not available yet.

Keywords: hydrops, anti-c, isoimmunisation, hemolytic disease of newborn.
**Introduction:** Hemolytic disease of newborn is a well recognised entity due to isoimmunisation of Rhesus (D) negative mother in Rh positive fetus. Severe degree of fetal hemolysis results in fetal hydrops. Although anti-Rh(D) was once the major etiology of hemolytic disease of the fetus/newborn (HDFN), the widespread adoption of antenatal and postpartum Rhesus immune globulin has resulted in a marked decrease in the prevalence of alloimmunisation due to the RhD antigen in pregnancy. Maternal alloimmunisation to other red cell antigens continues to play a role as the cause of fetal disease since no prophylactic immune-globulins are available to prevent the formation of these antibodies. Mild to severe cases of fetal hemolytic disease have been reported when antibodies such as anti-c, C, e, E or that of Kell, Kidd, Duffy, MNS, Lutheran, Diego, Xg, P and other private and public blood group systems found in sera of mothers. It is recommended that routine red cell antibody screening should be done at the first appointment in pregnant mothers and, if no antibodies are detected, once more in the third trimester between 28 and 36 weeks. The guidelines state that further testing is unnecessary, since immunisation during late pregnancy is unlikely to result in an antibody concentration sufficient to cause severe hemolytic disease of the neonate.

However, in India and other developing countries, at majority transfusion and antenatal care centres, routine antenatal antibody screening is done only for Rh (D) negative mothers to screen for Anti –D. Hence there may be a serious delay in diagnosing HDFN due to minor and other rarer antigens. First case of hemolytic disease of newborn due to anti-c antibodies from India was published in 2007. This was a retrospective diagnosis and fetal affection was of milder variety where baby was managed with intravenous immunoglobulin and phototherapy alone.

Here we report first case of antenatally diagnosed anti-c antibodies resulting in fetal hydrops which was of severe variety, requiring multiple in-utero and ex-utero transfusions.
Case Presentation: A 26 year old gravid-2 para-1 woman with no live issue was admitted under gastroenterology as a diagnosed case of extrahepatic portal vein obstruction with features of massive malena at 29 weeks period of gestation. She was referred for antenatal check-up to obstetric unit, where after clinical examination, ultrasonography was performed which revealed gross fetal hydrops. She was transferred to obstetric unit for further evaluation and management. Her prenatal course had been complicated by recurrent episodes of hematemesis and malena for past ten years and she had been diagnosed of having esophageal varices. There was a history of multiple blood transfusions and sclerotherapy sessions. Her first pregnancy was 2 years back (2006) in which she had regular supervised antenatal checkups in first and second trimester with a normal anomaly scan. Pregnancy was complicated by gestational diabetes mellitus, controlled on diet. There were episodes of recurrent malena in this pregnancy. Third trimester was unsupervised at home and patient was admitted at local private practitioner at the onset of labour. She underwent caesarean section for meconium stained liquor. Grossly normal male baby was born with jaundice at birth. Details of baby are not available but baby had received a blood transfusion on day 3 of life and expired on day 7.

Her present pregnancy was a spontaneous conception. Her first and second trimester antenatal checkups were with private practitioner at her hometown. She had presented in gastroenterology department in our institute at 29 weeks period of gestation with massive malena and anemia. Upper GI endoscopy revealed grade II esophageal varices for which sclerotherapy was done. Mother was given 3 units of packed red blood cells to raise the haemoglobin from 6 gm% to 10 gm%. On obstetric referral, ultrasonography at first visit at 30+5 weeks revealed severe fetal hydrops. Doppler studies were suggestive of fetal anemia. Mother was administered corticosteroids for fetal lung maturity. At 31 weeks, cordocentesis was done and intravascular intrauterine fetal transfusion with O negative cross matched blood was given. Since mother was Rhesus (D) O type positive, non-immune hydrops was suspected. Fetal blood was sent for blood grouping, hemoglobin and hematocrit, TORCH and Parvovirus B19 serology, hemoglobin electrophoresis, G6PD enzyme assay and karyotype. Fetal echocardiography was normal. Fetal blood group was ‘A’ positive and it was negative in work up for non immune hydrops. Maternal serum Indirect coomb’s test was positive leading to a suspicion of non anti-D antibodies. A special request was sent to blood bank to screen for uncommon minor blood group and non-D antibodies. Anti-c was detected in maternal serum in 1:4 dilution titre.
Maternal blood was resent to establish exact Rhesus haplotype and it was R1R1 (CDe/CDe). Fetus was monitored with biweekly biophysical profile and second intrauterine transfusion was given one week later with compatible O negative ‘c’ negative cross matched blood. At 32\(^{st}\) weeks, emergency caesarean section was done for poor biophysical profile.
A grossly hydropic female baby with a birth weight of 1.6 kg was born with massive ascites, hepatosplenomegaly, pallor and hypotonia. At birth, 150ml of ascitic tap was done and baby was shifted to nursery on bag and tube ventilation. Cord blood hematocrit was 15 and total serum bilirubin was 6.5mg/dl. Partial exchange transfusion followed by double volume exchange transfusion with O positive, c negative blood was done. Intravenous immunoglobulin in dose of 1gram/kg was administered post exchange. Baby required intense phototherapy for 4 days and by 2\(^{nd}\) week, developed conjugated hyperbilirubinemia due to inspissated bile syndrome which resolved on its own. Baby was then managed conservatively and discharged in stable condition on day 30 of life. Baby’s rhesus typing was refused by blood bank and was of no significance as baby had received two in-utero and two ex-utero transfusions.

Proposed fetal rhesus haplotype is cDe/cDe. The source of maternal isoimmunisation may be either fetomaternal haemorrhage in current or previous pregnancy or from multiple blood transfusions.
Discussion: Fetal hydrops may be immune or non-immune. Non immune hydrops results from reasons other than antigen-antibody incompatibility. Immune hydrops results from maternal antibodies capable of crossing placenta to react with fetal antigen and cause reaction manifesting as fetal hemolysis. In the largest retrospective review on etiology of hydrops, amongst 598 patients, cause of hydrops was unclear in 26.3% cases, isoimmunisation in 4.5 %cases and non immune etiology in 69.2 % cases. Amongst isoimmune causes, Rhesus antigens were responsible for 4.2%. There were only two cases due to non-Rh antigens, one each due to Kell and Duffy. There are 49 known rhesus antigens out of which 5 antigens c, C, D, e, E are well known. There is no small’d’ antigen. Besides this, there are other minor blood group systems like Kell, Duffy(Fy and FY), Kidd(JK and JK), M&N system. CDe is the most common haplotype in Caucasians (42%), Native Americans (44%), and Asians (70%) . Hemolytic disease of newborn has been reported due to Anti-c in various retrospective studies. The frequency of D and Non-D antigens differ in different populations with respect to ethnic origin. It is important to check that patients with anti-c should not have any additional antibodies, for although these might not compound any HDFN, they would certainly delay the provision of compatible blood for transfusion. Bowell et al (1986) observed a strong co-association of anti-c with anti-E in 41% of subject population. Perinatal mortality due to anti-c alone is usually much lower than that of Anti-D (1 in 250,000 vs 1 in 25,600 births respectively). However combination of anti-c and anti-E can cause severe fetal and neonatal hemolytic disease.

The management of anti-c isoimmunisation or isoimmunisation with any other irregular red blood cell antibody is similar to anti-D isoimmunised pregnancy, with specification that blood used for fetal/neonatal transfusion should be negative for respective antibody. Critical titer needs to be standardized with individual labs. In a series by Hackney et al, critical titre of 1:32 without supplementation with ultrasound and a critical titre of 1:16 supplemented with ultrasonographic features of hydrops was considered significant. In our case titer of 1:4 was associated with fetal hydrops and no other irregular antibody or cause of non immune hydrops could be attributed. There was a significant improvement in fetal and neonatal anemia following transfusion with c-negative blood, attributing it as the sole cause of fetal hemolysis and hydrops. However, fetal/neonatal direct coomb’s test (DCT) positivity doesn’t necessarily correlate with severity of hemolytic disease. DCT may be negative in anti-c isoimmunisation as this antibody is often present in small titers. Serologic evaluation of maternal antibodies,
hence, remains the cornerstone of management as approximately only 50% of antigen positive fetuses require more invasive testing\textsuperscript{11}.

Our experience in the management of case was similar to other authors\textsuperscript{3, 5, 11}. However, going with the modern era, instead of spectrophotometric evaluation of amniotic fluid $\Delta$OD 450 to assess fetal bilirubin due to severity of hemolysis; anemia was assessed using colour Doppler ultrasound and plotting peak systolic velocity of middle cerebral artery on Mari charts\textsuperscript{16}. However fetal anemia may not be severe enough to be detected by Mari’s criteria of middle cerebral artery peak velocity bringing in role of original Lileys curve and Queenan charts.

Through the presentation of this case, we want to emphasize the potentiality of immune hydrops due to irregular red blood cell antibodies. There is paucity of literature on prevalence of irregular antibodies in Indian population, despite one of highest obstetric load in world.

**Conclusions:** There is a need to impose properly formulated protocols to screen pregnant women with bad obstetric history with late trimester mishaps and pregnancies with fetal hydrops. Blood bank guidelines for screening of maternal serum antibodies and facilities for same need to be updated to decrease preventable perinatal morbidity and mortality.

**Competing interests:** The authors declare that they have no competing interests.

**List of Abbreviations:**
- HDFN; hemolytic disease of the fetus/newborn
- GI; Gastrointestinal
- G6PD; Glucose 6 phosphate dehydrogenase
- OD; Optical density
- DCT; Direct coomb’s test.

**Consent:** Written informed consent was obtained from the patient for publication of this case report

**Authors contributions:**
- SS assisted in the antenatal care of the mother, carried out the literature search and wrote the manuscript.
- SKJ, KKR, JBS and GK helped in managing the case and in final drafting the manuscript.
AS helped in post-natal care of the child, gave inputs in drafting the manuscript. All authors read and approved the final manuscript.

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