Rh isoimmunized pregnancy managed noninvasively: A report of two cases

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Abstract
Pregnancy with Rh isoimmunization is a grave situation. Two women with indirect Coombs test (ICT) positive were managed conservatively with a favorable outcome. Peak systolic velocity (PSV) of middle cerebral artery (MCA) was measured every 2 weeks, and pregnancy continued till the value remained <1.5 mean of median. In one woman, the pregnancy could be prolonged to 37 weeks when delivery was induced and the neonate did not develop hyperbilirubinemia. In the second woman with bad obstetric history, when a highly positive ICT was reported, intravenous immunoglobulin (IVIG) was given in a single dose of 5 g every 2 weeks starting at 27 weeks, for a total of three doses, along with measurement of PSV of MCA. Labor could be prolonged to 34 weeks when preterm spontaneous delivery occurred. The neonate could be salvaged with exchange transfusion and IVIG. The neonate is healthy with normal tone and no evidence of kernicterus.

Key words: Indirect Coombs test, intravenous immunoglobulin, mean of median, peak systolic velocity of middle cerebral artery, Rh isoimmunization

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Introduction
Rh isoimmunization is disastrous for a pregnant woman, and she often presents with repeated fresh stillbirths and recurrent pregnancy losses. If a Rh-negative woman reveals an indirect Coombs test (ICT) positive that is more than 1:32 titer, amniocentesis is performed and the optical density of amniotic fluid is determined by spectrophotometry. If bilirubin level is found to be in the danger zone as seen by plotting in Liley's or Queenan's curve, cordocentesis and fetal exchange transfusion are performed to manage these women and improve neonatal outcome.[1] However, with the advent of Doppler ultrasonography, these patients can be managed in a secondary care center, reducing cost and invasive interventional procedures. Intravenous immunoglobulin (IVIG) is another novel modality which is being combined with Doppler studies to further prolong pregnancy and reduce the occurrence or severity of hemolysis in the fetus.

Case Reports
Case 1
A 25-year-old gravida 2, para 1, abortion 0, woman presented with 5 weeks pregnancy. She earlier had a home delivery where the baby had severe birth asphyxia and did not survive. She was found to be normotensive, had a normal glucose challenge test, and was B Rh-negative. ICT was found to be negative. On inquiry, she revealed that anti-D immunoglobulin had not been given to her in the last delivery. She was prescribed tablet folic acid 5 mg and was followed up with regular antenatal checkups. At
28+ weeks of pregnancy, her ICT was found to be positive in a dilution of 1:64. She was called for a Doppler sonography and reported at 31+ weeks of pregnancy. The peak systolic velocity (PSV) of middle cerebral artery (MCA) was found to be 45 cm/s, corresponding to 1.0 mean of median (MOM). She was monitored with measurements of PSV of MCA every fortnightly and PSV remained below 1.3 MOM till 35 weeks of pregnancy [Table 1].

She was administered short-course betamethasone to prevent hyaline membrane disease, and elective induction of labor was performed at 36+ weeks of pregnancy.

A 2.25 kg male baby was delivered vaginally with a good Apgar score. The baby was O Rh-positive with hemoglobin 13.2 g. Cord blood bilirubin was 2.21 mg/dl and direct Coombs test was positive. At 24 h of birth, the bilirubin was still 3.20 mg/dl. Since significant hyperbilirubinemia did not occur, the baby thus was discharged.

Case 2
A 31-year-old woman presented with 7 weeks pregnancy. She was G8 P4 A3, i.e., gravida 8 para 4, abortions 3, with one female alive issue. Her first pregnancy was uncomplicated, but the baby died at 4 years of age. In the second pregnancy, a preterm delivery occurred and baby died because of jaundice and brain damage. The third pregnancy was a preterm twin delivery and the twins did not survive. In the fourth pregnancy, a female baby was delivered at 34 weeks but survived after two exchange transfusions. Thereafter, the woman had three consecutive pregnancy losses between 6 weeks and 5 months. Antepartum hemorrhage, hypertension, and congenital anomalies were not associated with these pregnancies. On examination, her blood pressure was 110/90 mmHg and she weighed 60 kg. On investigation, her blood group was B Rh-negative, hemoglobin 11 g%, glucose challenge test by O’Sullivan method showed blood sugar to be 120 mg%, thyroid-stimulating hormone 0.31 mU/ml, and anticardiolipin antibody and β2 glycoprotein were in the normal range. The ICT was negative.

The woman was started on folic acid, low dose aspirin 75 mg, and micronized vaginal progesterone 200 mcg by vaginal route daily. A viability scan showed 7 weeks viable fetus with no associated uterine anomaly or myoma. After 13 weeks pregnancy, the patient was started with iron with folic acid and calcium tablets. An anomaly scan at 17 weeks revealed a healthy fetus and 40 mm cervical length.

However, at 23 weeks, as ICT was repeated, it was found to be strongly positive, the ICT titer being 1:2038.

She accessed us with the report after 3 weeks at 26 weeks 6 days gestation on October 20, 2015.

The patient was sent for an ultrasound examination and a Doppler study. PSV of MCA was measured. The PSV-MCA at 27 weeks was 37 mm/s and its MOM was 1.29. The patient was monitored with measurements of PSV of MCA every 2 weeks [Figure 1]. The values of PSV were plotted on the nomogram proposed by Moise to know the MOM and thus judge the degree of anemia[21] [Figure 2]. Considering the very high ICT titer, the bad obstetric history suggesting Rh isoimmunization (neonatal hyperbilirubinemia and history of exchange transfusions in earlier births), IVIG was decided upon to improve neonatal outcome.

IVIG 5 g was first administered to her at 27 weeks of pregnancy. IVIG 5 g was repeated at 29 weeks and 31 weeks of pregnancy after PSV-MCA was determined and found to be < 1.29 MOM, i.e., zone C (normal hematocrit zone) [Table 2].

Hence, a total of three doses of IVIG were given at 2 weekly intervals. At 33 weeks, as the cervical length became 30 mm and imminent preterm labor was evident, short-course betamethasone was administered consisting of 12 mg in two doses at an interval of 24 h.

Preterm vaginal delivery occurred on December 20, 2015, at 34 weeks 2 days gestation.

A male baby weighing 2.5 kg was delivered with a good Apgar score and the baby was shifted to neonatal care unit. The baby was B Rh-positive, cord blood hemoglobin was 14 mg%, bilirubin was 6.5 g%, and direct Coombs test was positive. The serum bilirubin rose to 11 g% 6 h after birth when an exchange transfusion was performed. A dose of IVIG, 1 g/kg body weight was administered to the neonate. A repeat exchange transfusion was performed at 24 h after birth when serum bilirubin became 17 mg%. Another dose of IVIG was also repeated after 24 h of the first dose. Thereafter, the serum bilirubin started decreasing and the baby slowly recovered.

At 1 month of age, the infant has normal tone and normal reflexes. At 6 months of age, the baby has normal milestones with no neurological deficit.

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Table 1: Peak systolic velocity of middle cerebral artery at different gestational ages Case 1

| Date            | Gestational age | PSV of MCA (cm/s) | MOM of patient value | 1.5 MOM (cm/s) |
|-----------------|-----------------|-------------------|----------------------|----------------|
| August 27, 2015 | 31+             | 45                | 1.0 MOM              | 57.3           |
| September 15, 2015 | 33+            | 54                | <1.29                | 62.9           |
| September 23, 2015 | 35+            | 54                | <1.29                | 69             |

MOM: Mean of median; PSV: Peak systolic velocity; MCA: Middle cerebral artery
Rh isoimmunization pregnancies are now rare owing to the administration of anti-D after delivery, after abortion, and also prophylactic anti-D around 28 weeks of pregnancy. However, isolated cases are still being seen in India, where home deliveries sometimes occur in rural areas and anti-D is often forgotten.

Before the advent of Doppler ultrasonography, amniocentesis followed by spectrophotometric analysis to determine serum bilirubin level was the standard procedure, followed in Rh isoimmunized pregnancies. Vyas et al. first described the use of Doppler measurement of PSV of MCA to detect fetal anemia but succeeded in detecting anemia in only 50% pregnancies. In a recent study, MCA Doppler assessment was found to be superior to detection of fetal anemia with spectrophotometry of amniotic fluid using both Liley's and Queenan's curves. In another data analysis middle cerebral peak systolic velocity is effective for diagnosis of moderate to severe fetal anaemia and superior to amniocentesis for detection of fetal anaemia in case of red cell alloimmunization.

MCA Doppler graph was developed by Moise et al., based on gestational age, in which the degree of fetal anaemia could be assessed. Depending on the PSV of MCA at different gestational ages, three different zones C, B, A have been created corresponding to normal hematocrit, mild anemia, and moderate to severe anemia, respectively. In both our patients, 2 weekly PSV of MCA remained below 1.29 MOM, i.e., in C zone (normal hematocrit).

In Case 1, pregnancy could be prolonged to 37 weeks when elective termination was done. In Case 2, in which the ICT titer was very high, and IVIG was administered, spontaneous labor ensued at 34 weeks, while PSV-MCA was still in C zone.

In case of severe fetal anemia detected with PSV of MCA >1.5 MOM or by amniocentesis, intraperitoneal transfusion was the mainstay of fetal therapy after its introduction by Liley in 1963.

However, now with the help of real-time ultrasound, direct intravascular transfusion with O Rh-negative red cells is the preferred option of treatment.

IVIG has lately been used with success in several immune-mediated diseases in pregnancy such as alloimmune thrombocytopenia and idiopathic thrombocytopenia. A case with severe early-onset Rh sensitization has been treated with IVIG, early in 1997. In another study, maternal IVIG had shown some benefit in a severe case of hemolytic disease.

The exact mechanism of action of protection offered by IVIG is not clear. According to one study, it downregulates maternal antibody response, prevents transport of antibodies across the placenta, and blocks the destruction of fetal cells by occupying the Fc receptor site.

Lately, in a study, two Rh sensitized pregnant women were given IVIG. One woman accepted IVIG only up to 26 weeks and the second woman continued until 32 weeks. However, both the women had a favourable outcome with survival.
of both neonates. IVIG is an expensive formulation and the patients in the above study declined IVIG because of its high cost. The dose of IVIG used varies in different studies, and till date, no dose pattern has been decided upon. In the above study, 5–15 g was used depending upon the degree of hemolysis.[10]

In our patient Case 2, we used 5 g every 2 weeks, and despite the very high initial titer, the PSV-MCA remained below 1.29 MoM, i.e., C zone or normal hematocrit. We infer from this case study that 5 g given 2 weekly is a reasonable dose as in this patient pregnancy could be safely prolonged to 34 weeks in view of her earlier 3 consecutive losses before 24 weeks. Future research is required to optimize the dose of IVIG depending on the zone in which PSV-MCA falls in the Doppler graph or in other words the extent of hemolysis in the fetus.

In Case 2, the neonate was salvaged after delivery with exchange transfusion and adjunctive IVIG. Postnatal IVIG has been proved to be of benefit in hemolytic disease of the newborn. In a systematic review, it has been found to reduce the need for exchange transfusion and the duration of phototherapy in affected infants.[11]

**Conclusion**

Doppler measurement of PSV of MCA is a simple noninvasive technique of monitoring fetal anemia in Rh isoimmunized pregnancies. IVIG helps to further prevent hemolysis and when combined with PSV-MCA measurements, the duo can serve as an excellent treatment modality to avoid invasive interventions and referral to fetal medicine centers.

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**Conflicts of interest**
There are no conflicts of interest.

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