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The Role of Ultrasonography in the Non Invasive management of Rh ISO-Immunization – A Review from Case Reports

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Abstract: ***These three cases were examples of rhesus iso immunisation. All three cases were managed successfully using current conservative guides in ultrasonography for rhesus iso-immunization. The use of Uitrasound doppler had helped us to decide the timing and immediate neonatal management. In an ideal situation detection of fetal anaemia less than 9g/dl is an indication for intra uterine transfusion guided through cordocentesis. The transfusion is done using O Rh negative leucocytes depleted washed irradiated red cells crossed matched for maternal blood. However we are in the process of arranging this facility through national blood bank. At present we adopt a policy of cordocentesis for fetal Hb in suspected cases of fetal anemia and timely delivery while arranging the neonatal backup for exchange transfusion. This article further discusses the important aspects like pathophysiology, role of different Ultrasound scan parameters and their limitations.***

Keywords: Rhesus Iso- immunization, Ultrasonography Doppler velocities, non - invasive monitoring, Immune hydrops

1. Case 1

A 23 year old mother in her 2nd pregnancy presented at 34 weeks of gestation. Her blood group was B negative and her husband's blood group was B positive. Her first pregnancy resulted in a death in utero at 33 weeks and examination of the fetus had not revealed any reason to account for death in utero. Antibody screening had been negative during this pregnancy and she had been given one vial of Rhogam following the delivery of IUD.

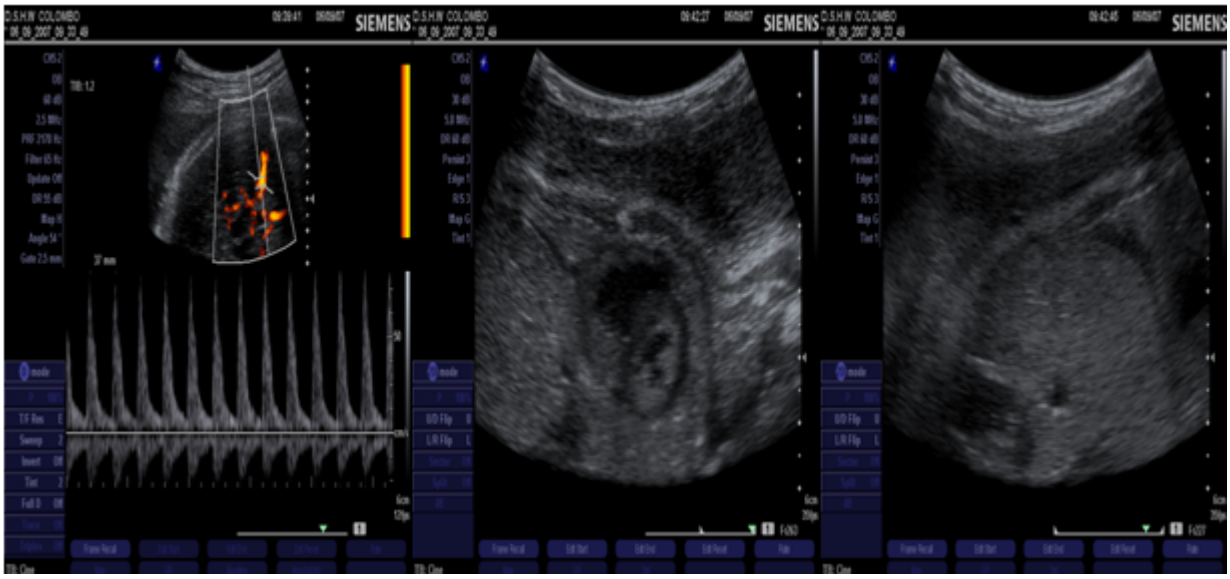
During this pregnancy she was positive for unexpected antibodies and antibody titre was 1 in 32 at 32 weeks. On admission at 33 weeks there was no ultrasound scan evidence of hydrops and the doppler studies were normal (non hyper dynamic) without evidence of fetal anaemia. Her antibody titre had risen to 1 in 512 by 34 weeks. Ultrasound scan showed evidence of early pericardial effusion and thin layer of fluid in the peritoneum. Middle cerebral artery showed hyper dynamic circulation. Immediate delivery was done at 36 weeks. Newborn haemoglobin level and total bilirubin levels were 9 g/dl and 5.75 mg/dl respectively. An exchange transfusion was done with double phototherapy. These values were 17 g/dl and 1.9mg/dl after exchange transfusion. Baby developed bile stained vomiting and abdominal distension on the second day which was managed conservatively after excluding a surgical pathology. The baby had received 07 days of neonatal care with phototherapy in the special care baby unit and had an eventful recovery.

2. Case 2

A 31 year old mother in her second pregnancy presented at 31 weeks. Her blood group was O negative while her husband's blood group was A Positive. She had delivered a baby with blood group A positive in her first pregnancy and that pregnancy had not been complicated with Rh sensitization. Her pregnancy records did not reveal any details of Anti D prophylaxis given to mother after first delivery. She was detected to have unexpected antibodies at 26 weeks with an anti D titre of 1 in 64. It had increased up to 1 in 256 by 30 weeks. Doppler studies detected evidence of hyperdynamic in the middle cerebral circulation. In addition there were evidence of early ascities and pericardial effusion but no change in fetal heart pattern. An amniocentesis done at 31 weeks elevation by two folds (photospectrometry) and cordocentesis showed fetal haemoglobin of 12g/dl. The pregnancy was continued up to at 34 weeks while being monitored for fetal anaemia, ductus venosus flow until the development of pericardial effusion, ascitis and abnormal heart patterns. Steroids completed and baby was delivered at 34+5 days. Immediate exchange transfusion was carried out as neonate's haemoglobin was 8g/dl. The baby had received 09 days of neonatal care with phototherapy in the special care baby unit and the recovery was uneventful

3. Case 3

A 28 yrs old mother presented in her 2nd pregnancy with a past history of hydrops IUD at 28 weeks in the 1st pregnancy and there were no details of antibodies levels nor antiD prophylaxis. Her antiD titre in the 2nd pregnancy at 28 weeks (late booking) was 1in 256 with a subsequent rise to 1 in 512 at 32 weeks. Her detailed Ultrasound scan showed high velocities in middle cerebral vessels, thoracic aorta with dilatation of the right heart, high pulsatility and reversed 'a' wave in the ductus venosus and pulsations in portal sinus. There was evidence of early pericardial effusion and ascitis. Steroids completed and baby was delivered at 32+5 days. Immediate exchange transfusion was carried out as neonate's haemoglobin was 7g/dl. The baby had received 14 days of neonatal care with phototherapy in the special care baby unit and had a good recovery.



4. Discussion

These three cases were examples of rhesus isoimmunisation. All three case were managed successfully non-invasively using current guides in Ultrasound scan for rhesus iso-immunization. Use of appropriate sonography has helped us to decide the timing and arrange the neonatal backup for further follow up. in an ideal situation detection of fetal anaemia less than 9g/dl is an indication for intra uterine transfusion using the same route for cordocentesis. The transfusion is made using O Rh negative leucocytes depleted washed irradiated red cells crossed matched for maternal blood. However we are in the process of arranging this facility through national blood bank. At present we adopt a policy of cordocentesis for fetal Hb in suspected cases of fetal anemia and timely delivery while arranging the neonatal backup for exchange transfusion. This article further discusses the important aspects like pathophysiology, role of different Ultrasound scan parameters and their limitations.

5. Pathophysiology

In red cell iso immunized pregnancies, maternal hemolytic antibodies cross the placenta and attach themselves onto fetal red cells, which are then destroyed in the fetal reticulo-endothelial system. In mild to moderate disease there is a compensatory increase in intramedullary erythropoiesis, and in severe disease there is recruitment of extramedullary erythropoietic sites, such as liver and spleen.

Fetal blood pO2, pCO2 and pH usually remain within the normal range except in extreme anemia, when hypoxia and acidosis occur. The fetal blood oxygen content decreases in proportion to the degree of anemia. The fetal 2,3-diphosphoglycerate (2,3-DPG) concentration is increased and the consequent decrease in hemoglobin–oxygen affinity presumably improves delivery of oxygen to the tissues. In moderate anemia, the umbilical arterial plasma lactate concentration is increased but this is cleared by a single passage of fetal blood through the placenta and normal umbilical venous levels are maintained. In severe anemia, when the oxygen content is less than 2 mmol/l, the placental capacity for lactate clearance is exceeded and the umbilical venous concentration increases exponentially. These data suggest that, in the fetus, systemic metabolic acidosis can be prevented, unless the oxygen content decreases below the critical level of 2 mmol/l.

5.1 When the fetal hemoglobin concentration deficit exceeds 6 g/dl, hydrops fetalis develops.

This may be the result of extensive infiltration of the liver by erythropoietic tissue, leading to portal hypertension, due to parenchymal compression of portal vessels, and hypoproteinemia, due to impaired protein synthesis. Furthermore, at this hemoglobin concentration deficit, the oxygen content decreases below the critical level of 2 mmol/l.

5.2 Diagnosis and treatment of fetal anemia

The severity of fetal hemolysis can be predicted from:
(1) The history of previously affected pregnancies;
(2) The level of maternal hemolytic antibodies;
(3) Changes in the flow velocity waveforms obtained by Doppler studies of the fetal circulation;
(4) The altered morphometry of fetus and placenta;
(5) The presence of pathological fetal heart rate patterns.

However, there is a wide scatter of values around the regression lines describing the associations between the degree of fetal anemia and the data obtained from these indirect methods of assessment. The only accurate method for determining the severity of the disease is blood sampling by cordocentesis and measurement of the fetal hemoglobin concentration. cordocentesis should be performed for all patients with a history of severe disease and those with a hemolytic antibody level of more than 15 IU/ml or a titer of 1 in 128 or more. At cordocentesis, a fetal blood sample is first obtained and the hemoglobin concentration is determined. If this is below the normal range, the tip of the needle is kept in the lumen of the umbilical cord vessel and fresh, packed, rhesus-negative blood compatible with that of the mother is infused manually into the fetal circulation through a 10ml syringe or a transfusion set. At the end of the

transfusion, a further fetal blood sample is aspirated to determine the final hemoglobin concentration. Subsequent transfusions are given at 1–3-weekly intervals until 34–36 weeks, and their timing is based on the findings of non-invasive tests, such as Doppler studies, and the knowledge that, following a fetal blood transfusion, the mean rate of decrease in fetal hemoglobin is approximately 0.3 g/dl per day.

6. Doppler Studies

6.1 Uterine artery

In a longitudinal study of 12 fetuses, Copel et al. included the uterine artery pulsatility index (PI), together with the descending thoracic aortic peak velocity, in a multiple regression model to predict whether the fetal hematocrit was below or above 25% before the second fetal blood transfusion. The authors suggested that the significant contribution of uterine artery PI to the model could be explained by the effect of resolving placental edema after the correction of fetal anemia by the second transfusion. However, this is unlikely because there was no difference in uterine PI between hydropic and non-hydropic fetuses. Therefore; it is unlikely that fetal anemia alters the uteroplacental circulation.

6.2 Umbilical artery

Rightmire et al. found a significant inverse correlation between impedance to flow in the umbilical artery and fetal hematocrit. It was suggested that increased impedance to flow in the fetoplacental microcirculation may be due to hypoxemia-mediated capillary endothelial cell damage or clogging of the placental capillaries by the large fetal erythroblasts. In contrast, Warren et al. reported that impedance in the umbilical artery was not abnormal in red cell isoimmunized pregnancies with high amniotic fluid bilirubin concentration. Similarly, in a study of 95 affected pregnancies, umbilical artery PI, measured immediately before cordocentesis, was not increased and was not associated with fetal anemia.

6.3 Impedance to flow in fetal vessels

Vyas et al. measured the PI in the middle cerebral artery of 24 non-hydropic fetuses from red cell isoimmunized pregnancies; there were no significant associations between PI and either the degree of fetal anemia or the degree of deficit in oxygen content measured in samples obtained by cordocentesis. Furthermore, in a study of 95 fetuses undergoing cordocentesis for rhesus disease, the PI in both the middle cerebral artery and descending thoracic aorta was not significantly different from normal controls and there was no significant association between PI and fetal anemia. These findings indicate that impedance to flow is not affected by anemic hypoxia and by the alterations of blood constituents, such as hypoproteinemia, or red cell morphology, such as erythroblastemia, that accompany severe anemia.

6.4 Fetal cardiac Doppler studies

Meijboom et al. measured maximal and mean temporal velocity and early passive to late active ventricular filling phase (E/A) ratio on the atrioventricular orifices in 12 fetuses immediately before fetal blood transfusion. There was a non-significant increase in both maximal and mean temporal velocities. Furthermore, there was a significant reversal in the E/A ratio in the flow waveforms from the tricuspid valve. In normal fetuses, these two peaks present an ‘M’ shape, whereas in anemic fetuses the E peak is dominant, suggesting that, in fetal anemia, there is an increased pre-load in the right atrium. Copel et al. found that anemic fetuses before any intrauterine transfusion had significantly higher stroke volumes and ventricular outputs than normal controls. The increase was shared proportionately by both ventricles. Extremely compromised fetuses demonstrated diminished cardiac function as a terminal finding.

In an extended series of 95 previously untransfused fetuses undergoing cordocentesis for rhesus disease, there was a significant increase in aortic velocity with the degree of fetal anemia. Although, in some hydropic fetuses, aortic velocity was decreased, in the majority of cases the velocity was increased. In an additional series of 212 fetuses that had a transfusion 2–3 weeks previously, the relation between aortic velocity and anemia was weaker.

There was a significant association between the degree of fetal anemia and the increase in blood velocity. Some authors speculated that this increase in common carotid artery velocity reflected increased cardiac output associated with fetal anemia, rather than a chemoreceptor mediated redistribution in blood flow, as seen in hypoxemic growth-restricted fetuses.

Mari et al found a significant association between the peak systolic velocity in the middle cerebral artery and fetal hematocrit at cordocentesis. In a prospective study of 16 fetuses from isoimmunized pregnancies, they found that all the anemic fetuses had peak velocity values above the normal mean for gestation, whereas none of the fetuses with peak velocity below the normal mean was anemic. On the basis of these results, they suggested that, in the management of isoimmunized pregnancies, the indication for cordocentesis should be a peak systolic velocity above the normal mean for gestation. These results were confirmed in a multicenter study involving 111 fetuses from isoimmunized pregnancies; all moderately or severely anemic fetuses had increased peak velocity in the middle cerebral artery.

6.5 Blood Velocity in Fetal Veins

Rightmire et al. studied 21 previously transfused fetuses from red cell isoimmunized pregnancies, reported increased peak systolic and time averaged maximum velocities in the ductus venosus before intravascular fetal blood transfusion, which returned to normal values the following day.

It was suggested that the increase in ductus venosus blood flow in anemic fetuses reflects increased venous return and

therefore cardiac preload. Hecher et al. recorded flow velocity waveforms from the ductus venosus, right hepatic vein, inferior vena cava, middle cerebral artery and descending thoracic aorta from 38 red cell isoimmunized pregnancies and found that only the velocity in the thoracic aorta was significantly associated with the degree of fetal anemia. Furthermore, this study showed that heart failure is not the primary mechanism for the development of hydrops, but rather the end-stage of severe anemia, because the pulsatility of venous blood flow waveforms was not increased. Hydrops may be due to reduced colloid osmotic pressure, hypoxia-induced endothelial damage and increased permeability. Severe fetal anemia, with consequent cardiac failure, is associated with a reversed 'a' wave in the ductus venosus. Under these conditions, pulsations are also present in the venous portal system (which in normal fetuses is characterized by a continuous flow). The pulsatile pattern present in the venous system corresponds to findings in children with portal hypertension. Since, in fetal anemia, resistance to flow in the fetal circulation and placenta is unchanged, an increase of umbilical venous blood flow is in accordance with high cardiac output and elevated arterial velocities.

6.6 Hemodynamic changes following fetal blood transfusion

Warren et al. and Kirkinen et al. found that, immediately after a fetal intraperitoneal blood transfusion, there was a temporary increase in umbilical venous blood flow and subsequent gradual decrease from above to within the normal range. It was suggested that the gradual decrease in flow, coinciding with resolution of fetal ascites, was the result of absorption of the transfused blood and correction of the fetal anemia. Similarly, Mari et al. found that intrauterine transfusion is associated with a significant decrease in the peak velocity in the middle cerebral artery and this decrease is proportional to the increase in fetal hematocrit. These findings are likely to be the result of a decrease in cardiac output following the transfusion due to:

1) Increased blood hemoglobin concentration and viscosity, and consequent decrease in venous return;
2) Congestive heart failure due to overloading of the fetal circulation; or
3) Cardio-inhibition due to increased baroreceptor activity.

The most likely explanation for these findings is that transfusion results in temporary cardiovascular overload. Animal studies have also shown that the fetal heart has very limited reserve capacity to increase its output in response to acute overload, and that massive increases in fetal blood volume are associated with a decrease in cardiac output. After transfusion, there is a rapid rate of fluid loss and this explains the rapid recovery in cardiac output

6.7 The role of amniocentesis in management of Rh sensitized pregnancies

Bevis D.C.A in 1952 has 1st done the amniocentesis in the management of Rh disease of the newborn. Liley in 1961 assessed the progress of the disease by serial amniocentesis by using amniotic fluid billirubin levels detected by optic density at 450. A need for fetal transfusion was determined by plotting photo spectrometry values in a chart and the presence of early fetal ascitis. Several refinements of the Liley's chat has been published (Whifield 1970). Nevertheless the photo spectrometry billirubin levels seemed to be less reliable indirect predictors of fetal anemia especially before 28 weeks and in the presence of anti-kell antibodies. This has prompted some units to abandon the amniocentesis based diagnosis and rely exclusively on invasive and non invasive monitoring of fetal anemia. (Nicolaides at el. 1984).

7. Conclusion

Despite wide spread Rhesus prophylaxis still there are cases of isoimmunisation due to poor attention on Rh status of the mother. This needs further strengthening of our care at all levels in obtaining a proper clinical history and obtaining blood group and Rh status. USS has become one of the frontiers in the non invasive management of this condition with different variable with different merits. In the pathophysiology red cell isoimmunized pregnancies, placentation is normal and therefore indices of impedance to flow in the uterine and umbilical arteries are normal, irrespective of the severity of fetal anemia.
In red cell isoimmunized pregnancies, normal placental perfusion results in normal fetal blood pO2, pCO2 and pH and therefore there is no evidence of redistribution in the fetal circulation; the PI in the middle cerebral artery, thoracic aorta and renal arteries is normal.

In red cell isoimmunized pregnancies, the left and right cardiac outputs and blood velocity in the umbilical vein, middle cerebral artery, thoracic aorta, renal arteries and the fetal venous system are increased in proportion to the degree of fetal anemia.
The most likely mechanism for the hyperdynamic circulation of anemic fetuses is decreased blood viscosity, leading to increased venous return and cardiac preload.

In red cell isoimmunized pregnancies, fetal heart failure is not the primary mechanism for the development of hydrops. However, severe anemia with consequent end-stage cardiac failure may be associated with high pulsatility or even reversed 'a' wave in the ductus venosus and pulsations in portal sinus.

In red cell iso immunized pregnancies, intravascular fetal blood transfusion results in temporary cardiovascular overload with a temporary fall in both right and left cardiac outputs. The place for serial amniocentesis is limited in current practice due to its poor correlation with fetal anemia.

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