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Successful Management of Rh Isoimmunized Pregnancies at a Tertiary Care Centre-Our Experience

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Abstract

Alloimmunization, often called Rh-isoimmunization, was first described in Rh negative women with an Rh-positive fetus, but it can occur with many other blood type incompatibilities. It is a condition that may occur during pregnancy when there is an incompatibility between mother's blood type and fetus blood type. During pregnancy, red blood cells from fetus can cross placental barrier and there is formation of antibodies. Those antibodies can cross back through the placenta and destroy fetal RBCs causing fetal anemia and fetal hydrops. This is called hemolytic disease of the fetus.

Still the fetal anemia due to red cell alloimmunization in Rh isoimmunized pregnancy is the leading cause of intra-uterine blood transfusion. However intra-uterine transfusion can be considered in severe fetal anemia of any other cause like Parvo B 19 viral infection. Access of umbilical vein also helps in transfusion of platelets in alloimmune thrombocytopenia and injection of drugs to fetus like anti-arrhythmic drugs in fetal arrhythmia. Ultrasound guided access of umbilical vein is common for all type of intra-uterine transfusion.

We managed Rh isoimmunized pregnancies at our centre by intrauterine transfusions and even conservatively.

Keywords: Rh isoimmunization; Intrauterine transfusion; Phototherapy; Exchange transfusion

Introduction

Maternal Rhesus (or red cell) isoimmunization occurs when a pregnant woman develops an immunological response to a paternally derived red blood cell antigen (D) foreign to the mother and inherited by the fetus. The antibodies may cross the placenta, bind to antigens present on the fetal erythrocytes and cause hemolysis. Hemolysis of the erythrocytes cause anemia in the fetus, and if severe, may result in edema, hydrops fetalis, and even fetal death. Hemolytic disease of the fetus/neonate can also be caused by other antigens of the Rh blood group system (the Rh blood system consists of the C, c, D, E, e, and G antigens - there is no d antigen) and by the so-called 'irregular antigens' of the non-rhesus blood group system such as Kell, MNS, and Kidd [1]. Therefore, the term red cell or Rhesus alloimmunization is more commonly used.

Onset of fetal anemia

Hemolytic disease of newborn was one of the most common causes of early neonatal death before 1960. Preterm delivery and followed by exchange transfusion were the only treatments available until in 1960s. Freda and colleagues performed open fetal surgery, transfusing the fetus using a vein in the exteriorized leg [2]. A major breakthrough was the development of per-cutaneous intra-peritoneal transfusion under X-ray guidance by Sir William Liley [3]. However, hydropic fetuses did not take up the transfused blood from the peritoneal cavity very well. In addition, the technique was not feasible before 27 weeks' gestation [4]. In the 1980s, Sir Charles Rodeck introduced the technique of intravascular transfusion by needling the umbilical artery under direct fetoscopic guidance [5]. Shortly afterwards, Jens Bang in Denmark and Fernand Daffos in France both pioneered fetal blood sampling under ultrasound guidance. In the last two decades, their approach is still used worldwide as the technique for intrauterine transfusions [6,7].

Still the fetal anemia due to red cell allo-immunization in Rh isoimmunized pregnancy is the leading cause of intra-uterine blood transfusion. However intra-uterine transfusion can be considered in severe fetal anemia of any other cause like Parvo B 19 viral infection. Access of umbilical vein also helps in transfusion of platelets in alloimmune thrombocytopenia and injection of drugs to fetus like anti-arrhythmic drugs in fetal arrhythmia. Ultrasound guided access of umbilical vein is common for all type of intra-uterine transfusion.

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Table 1: Expected Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery as follows.

Multiples of median				
	1.00 (Median)	1.29	1.5	1.55
POG	Peak systolic velocity			
18	23.2	29.9	34.8	36
20	25.5	32.8	38.2	39.5
22	27.9	36	41.9	43.3
24	30.7	39.5	46	47.5
26	33.6	43.3	50.4	52.1
28	36.9	47.6	55.4	57.2
30	40.5	52.2	60.7	62.8
32	44.4	57.3	66.6	68.9
34	48.7	62.9	73.1	75.6
36	53.5	69	80.2	82.9
38	58.7	75.7	88	91
40	64.4	83	96.6	99.8

Diagnosis of fetal anemia

All Rh isoimmunized patients who have been transferred to our centre were followed with MCA PSV at our Obstetrics unit and values tallied with standard chart as per the period of gestation. Patients with MCA PSV values less than 1.0 MoM and between 1 to 1.29 MoM were called up after two weeks for repeat sonography for MCA PSV, but patients with values between 1.29 to 1.5 MoM were called up after a week only for repeat MCA PSV. Along-with MCA PSV monitoring fetus was also screened for any sequela of iso-immunization in the form of cardiomegaly and ascites/hydrops. Weekly ultra-sonographic evaluation is important for early detection of fetal hydrops when MCA PSV is between 1.29 to 1.5 MoM or above. When fetal Hb percentage drops below 5 g/dl features of hydrops develop. So, hydrops is a sign of severe fetal anemia and is usually associated with adverse neonatal outcome. The first sign of hydrops due to fetal anemia is ascites which initially starts as a rim of fluid around abdomen and pericardial effusion practically always in conjunction with cardiomegaly. If cardio-thoracic ratio was 0.6 or above, it is labeled as cardiomegaly. Skin edema develops later and pleural effusions are signs of advanced disease. Even increased placental thickness and poly-hydramnios were looked for in the sonography in such fetuses. Some severely hydropic anemic fetuses may even develop oligohydramnios. Fetal movements are sometimes remarkably normal despite severe anemia. CT ratio more than 0.6 is diagnostic of fetal cardiomegaly and thin rim of fluid in fetal abdomen more than 3 mm is suggestive of developing ascites and fluid in more than one body cavity implies hydrops.

So, USG can be used to diagnose fetal anemia based on above parameters. Treatment modalities at this juncture with the patient are either to undergo intrauterine blood transfusion to prolong the gestation or deliver the fetus immediately and later manage the new-born with either exchange transfusion or IV Ig & phototherapy or only observation if no signs of fetal anemia. We had one patient managed only with monitoring MCA PSV. A 26 years (case no 4) old patient was referred from a peripheral hospital at 33 weeks 5 days' gestation with ICT titer of 1:16. Two weekly USG was done for MCA PSV, Fetal Hydrops & Fetal cardiomegaly and blood test repeated for ICT titer. Patient was monitored till 36 weeks but there was no rise of ICT titer and MCA PSV was between 1.29 to 1.5 MoM and fetus did not have hydrops or cardiomegaly. Patient delivered a male baby at 36 weeks with birth weight of 2.5 kg and with Hb of 11.8 gm%. Neonate did not require exchange transfusion and discharged after 2 weeks of observation in NICU. Two more such patients (case no 4&5) was only observed with MCA PSV and delivered without intervention with good neonatal outcome (Table 1).

When to go for Intra-uterine transfusion in such cases

As in all surgical procedures performed by clinicians, the technical details are only part of the clinician's skill. The correct indication and timing are very much important especially in invasive procedures in obstetrics, in which any complication is potentially lethal for the fetus. A careful identification of individual fetus at risk for anemia requiring intrauterine transfusion can be picked and treated within time. However, not all fetuses in allo-immunized pregnancies develop severe anemia. Serial assessment of signs of anemia like rising MCA PSV, Cardiomegaly or Hydrops is necessary to enable timely intervention. The goal and the challenge is to transfuse only in case of severe anemia, but before the fetus develops hydrops. Survival after intrauterine transfusion in hydropic fetuses is significantly lower compared to non-hydropic fetuses [8]. Several studies have shown that hydrops only develops when the fetal hemoglobin drops to levels 6-7 SD below the mean for the gestational age. Ideally, a transfusion is given when MCA PSV is more than 1.5 MoM and before appearance of fetal ascites. In such cases, one can transfuse a relatively large amount of O-negative doubly irradiated donor blood, which is not hemolysed by the red cell antibodies. The next transfusion can then be given several weeks later. Further we will discuss when to transfuse next?

How much blood volume to transfuse

The volume of packed cells to be given (V) was calculated using the formula (Moise et al., 1997)

V=FPV (Ht target - Ht first sample) Ht donor blood,

FPV (Feto-Placental blood Volume) = 1.046 + (0.14 × ultrasound estimated fetal weight (g))

Technique of transfusion

At our hospital we don't have irradiator machine so blood has been arranged from other hospital and it has to be transfused within 12 h of issue. Ideally intrauterine transfusion should have a team and each member of team should know his or her responsibility and it requires a good quality ultrasound machine. We have a designated team in OT and each member is briefed time and again for orientation of job which they have been assigned. The most effective and common site for transfusion is umbilical vein at site of insertion of umbilical cord at placenta. If we try in free loops, chances of tear of umbilical cord is high.

Before starting the procedure, we should know the placental location. In our centre if placenta was anterior, fetus was not paralyzed but in case of others where placenta is posterior fetus was paralyzed before transfusion by pancuronium or vecuronium so that fetus does not disturb the on-going procedure.

The fetal medicine specialist actually puts the needle in the fetal umbilical vein at insertion site under ultrasound guidance. One assistant usually the second gynecologist actually connects the three-way connector and two more assistants are detailed for pushing blood. Fetal medicine specialist who has inserted needle is stabilizing needle when the blood is being pushed and he continuously monitors

Table 2: Preparation of blood for fetal transfusion.

Plasma reduced (haematocrit 0.7 - 0.85)
In Citrate Phosphate Dextrose (CPD) anticoagulant (theoretical risk of toxicity from additive solutions)
Leucocyte-depleted
Less than 5 days old (to avoid hyperkalaemia)
Cytomegalovirus (CMV) antibody negative
Sickle screen negative
Irradiated to prevent TA-GvHD (shelf life 24 hours)
Usually group O with low-titre haemolysins (or ABO identical with the fetus)
RhD and Kell negative and red cell antigen negative for maternal alloantibodies
Indirect Antiglobulin Test (IAT) crossmatch compatible with the mother's plasma

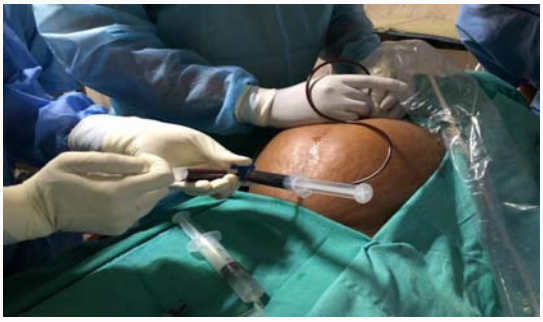

Figure 1: Picture demonstrating the process of IUT being done under aseptic conditions in OT at our centre.

fetal heart rate for any distress during the procedure. One assistant is detailed to assist with the various medications and syringes and another assistant helps to perform the on-site blood tests and calculation [9,10]. In general, fetal blood transfusions including all preparations take 40 min to 60 min and can be carried out as outpatient procedure or with an overnight stay. At our centre, we perform procedure in afternoon as are dependent for blood and we usually get blood in afternoons only and we discharge the patient either the same evening or the next morning (Figure 1).

Instruments required

USG machine with Doppler, 20 Gauze spinal needles for fetal paralysis, 22 Gauze spinal needles for insertion in umbilical vein, ten 10 ml syringes for pushing blood, 50 cm three-way connector.

Fetal paralysis

Fetus was not paralyzed where placenta was anterior but usually done in case of posterior placenta using diluted pancuronium or vecuronium (intramuscular in thigh) depending upon the availability (Table 2).

A 26 years old patient with 25 weeks gestation with previous one neonatal death due to kernicterus. On arrival, ICT was 1:128. USG was performed, MCA PSV was more than 1.5 MoM and there was gross cardiomegaly and gross fetal hydrops. Patient underwent intrauterine transfusion seven times. After fourth intrauterine transfusion hydrops completely resolved as shown in pictures below. Pre-transfusion cordocentesis sample had a hematocrit of 9 and Hb 3 gm% and post transfusion of last intrauterine transfusion was 45. Patient delivered at 36 weeks 2 days with a Hb of 15 gm%. There was no need of exchange transfusion or phototherapy. Neonate was monitored in postnatal ward with mother and discharged after one week (Figures 2-5 and Table 3).

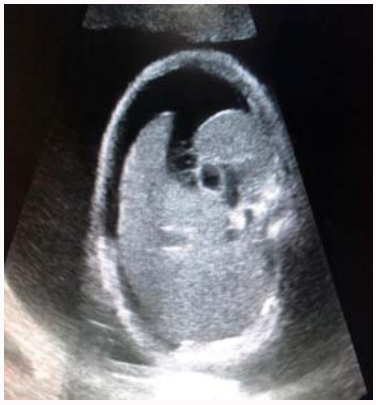

Figure 2: Gross fetal ascites.

Donor blood

The primary source of blood for intrauterine transfusion is O-negative with low titer hemolysins, unrelated donor blood and blood should be less than 5 days old to prevent hyperkalemia. The blood has been collected within 24 h and IAT cross-matched compatible with the maternal blood. It should have been screened for hepatitis B and C, cytomegalovirus and HIV and it should be RhD and kell negative as well as irradiated to remove the white blood cells to avoid 'graft *vs.* host 'like complications in the fetus and that is why it has to be transfuse within 24 h of irradiation. The blood is packed to a hematocrit of 75% to 85% to minimize the volume of blood that needs to be transfused to prevent volume overload.

Maternal blood is also a good source of blood for intrauterine transfusions. It has the theoretical advantage of decreasing the risk for sensitization to new red cell antigens. In addition, a longer circulating half-life can be expected because of the fresh source of cells. Parents seem to have some preference for the use of mothers' own blood to be donated to the fetus. However, the blood must undergo rigorous testing for antibodies against the infectious diseases mentioned earlier. For logistic reasons, we have therefore chosen to use unrelated donor blood. A study comparing the fetal effects of maternal red cells *vs.* unrelated donor cells showed no significant differences in decline rate of red blood cells until 33 weeks gestation [11].

Timing of subsequent transfusions

The second transfusion usually has to be performed 2 to 3 weeks after the first transfusion or earlier if the desired post-transfusion hematocrit has not been reached. The mean fall in hematocrit is around 1% per day, but there is a wide variation (SD 0.44). This

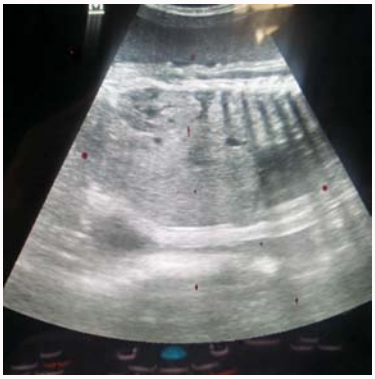

Figure 3: Resolved fetal ascites after multiple transfusions.

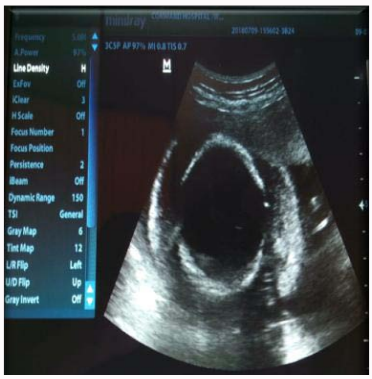

Figure 4: Gross fetal scalp edema.

donor cell fall is due mainly to growth of the fetus with increasing feto-placental volume and only partly because of actual destruction of red cells. This rate of fall is quite unpredictable between the first and second transfusion because at this stage, the percentage of fetal erythrocytes in the fetal circulation and the suppression of erythropoiesis are variable. After the second transfusion, the mean fall in hematocrit is generally better to predict because at this stage, almost all of the fetal erythrocytes are replaced with donor erythrocytes and the erythropoiesis is almost completely suppressed. After the second transfusion, the interval can safely be 4 or even 5 weeks if the hematocrit after transfusion is at least 45%. In general, transfusions are performed until the gestational age of 35 weeks is reached [12]. This means that a pregnancy in which transfusions are performed can be continued until approximately 37 weeks, thereby reducing the risks of respiratory and other prematurity problems. Several groups have published their experience showing that repeated intravascular transfusions throughout pregnancy are associated with survival rates ranging from 76% to 96% [13].

Post-transfusion care

We practice intrauterine transfusion in operating room after 26 weeks so that immediately procedure induced fetal distress can be tackled simultaneously. After the transfusion, patient is shifted to labor room where strict monitoring of fetal heart rate is done. The woman is advised to rest on her left lateral position for one hour to optimize blood flow to and from the uterus. She then remains in bed until all effects of the sedatives have gone usually 2 h to 4 h and by that time, she starts perceiving fetal movements. After this the patient is shifted to obstetrics ward and subsequently discharged to home the same or the next day. A follow-up appointment is typically scheduled after 10 to 12 days.

We happened to manage 3 such iso-immunized pregnancies (case no 1, 2 and 7) at our centre using intra-uterine transfusions. First (case no 1) we have discussed in detail above. Two more patients were monitored with MCA PSV and intrauterine transfusion was done when MCA PSV became more than 1.5 MoM (at 35 to 36 weeks) and delivered with good outcome (Table 4,5).

Exchange transfusion

The use of ET (also known as exsanguination, venesection, or substitution transfusion) was foremost reported by Dr AP Hart in 1925 in a severely jaundiced neonate with erythroblastosis fetalis. He used the sagittal sinus for removing blood while infusing it through a peripheral venous cut-down. Louis Diamond [14] was the pioneer to utilize the umbilical vein for ET in 1946. He provided the complete technique and apparatus required for performing ET.

Over the past few decades, development and widespread use of rhesus immunoglobulin, intra-uterine transfusion, improvement in diagnostic prenatal ultrasound, intensive phototherapy and use of intravenous immunoglobulin, has resulted in progressive reduction for the need of ET. Ante-natal serial measurement of anti-D antibody levels, assessment of Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) can predict the risk of severe hemolytic disease and the need of ET in a neonate.

An exchange transfusion involves removing aliquots of patient blood and replacing with donor blood in order to remove abnormal blood components and circulating toxins whilst maintaining adequate circulating blood volume. It is primarily performed to remove antibodies and excess bilirubin in iso-immune disease, the incidence of exchange transfusion is decreasing secondary to the prevention and improved prenatal management of allo-immune hemolytic disease and improvements in the management of neonatal hyper-bilirubinemia.

We had a similar scenario (case no 3) at our centre where in a 28-year-old second gravida with 30 weeks pregnancy was referred

Table 3: Schedule of intrauterine transfusion done in this hydropic fetus at our centre.

POG	PRE-TRANSFUSION HCT	PRE-TRANSFUSION MCA PSV	POST- TRANSFUSION HCT	POST- TRANSFUSION MCA PSV
25 weeks 04 days	9	62.5	14	57
26 weeks 04 days	10.8	60	20.7	54
26 weeks 06 days	18	56	25	50
27 weeks 03 days	22	52	33.6	48
28 weeks 03 days	25.7	50	43.5	45
30 weeks 06 days	34.1	48	49	42
33 weeks 6 days	35.1	48	45	40

Table 4: Ante- natal profile of all Rh iso-immunised patients treated at our centre.

Case No	Gravida	Age	POG & ICT Titre when reported		Previous any bad obstetric outcome	MCAPSV (MoM)	Cardiomegaly	Fetal Hydrops	IUT	IVIG Mother
1	G4P3L2	26	26 Weeks	1:128	Previous one neonatal death by kernicterus	>1.5	Yes	Present	Yes (seven times)	No
2	G4P3L3	29	24 Weeks	1:32	Nil		Mild cardiomegaly	No	Yes (one time)	No
3	G2P1L1	28	30 Weeks	1:32	Nil	1.29-1.5	Yes	No	No	No
4	G3P2L2	26	33.5 Weeks	1:16	Nil	1.29-1.5	No	No	No	No
5	G3P2L1	31	34 Weeks	1:32	Nil	>1.5	Yes	No	No	No
6	G3P1L1A1	32	7 Weeks	1:64	Hydrops at 18 weeks in previous pregnancy, spontaneous abortion	Followed up with MCA PSV	No	No	NO	Yes 3 doses
7	G2P1L1	33	30	1:64	Nil	Followed up with MCA PSV	Mild cardiomegaly	No	One time	No

Table 5: Neonatal outcome.

Case no	Delivered at POG	Exchange transfusion	Phototherapy	IVIG Mother	IUT	IV IG to neonate	Discharged at day of life
1	36 weeks 2 days	No	No	No	Yes	No	7
2	34 weeks 6 days	No	Yes	No	Yes	No	7
3	35 weeks 3days	Yes	Yes	No	No	No	24
4	36 weeks	No	Yes	No	No	No	14
5	34 weeks 3 days	No	Yes	Yes	No	Yes	29
6	35 weeks 5 days	No	Yes	No	No	No	10
7	36 weeks	No	Yes	No	Yes	No	13

with a ICT titer of 1:32. Patient was followed by MCA PSV weekly and USG for fetal hydrops and cardiomegaly. Till 35 weeks MCA PSV was between 1.29 MoM-1.5 MoM and after 35 weeks the MCA PSV became more than 1.5 MoM with no features of hydrops but with mild fetal cardiomegaly. IUT was not performed in this case as there was no severe fetal anemia till 35 weeks. Patient was delivered at 35 weeks 3 days. Female neonate with birth weight of 2.2 kg had Hb of 10.5 gm% & was observed in NICU. On day 3 baby started having increase in serum bilirubin from 3.5 to 8 and there was drop in Hb%. Exchange transfusion was done in NICU once with intermittent phototherapy. After 23 days of observation in NICU, baby was discharged with an Hb of 13 gm% and with normal bilirubin.

IVIG treatment

Maternal D allo-immunization detected in early gestation requires aggressive intervention to prevent severe fetal anemia. An Intrauterine Transfusion (IUT) is indicated to prevent fetal death once severe fetal anemia has been detected, but is not without risks. Role of Intravenous Immunoglobulin (IVIG) have been described, but they usually bridge to IUT. At our centre, we successfully managed a patient (case no 6) with maternal IVIG where in a 32 years old G3P1L1A1was referred to our hospital at 7 weeks POG (with ICT titer of 1:64) with history of fetal hydrops at 18 weeks in second pregnancy and spontaneous abortion while she was being work up for intrauterine transfusion. This time McDonald's cervical encirclage was applied at 13 weeks in view of short cervix and was monitored with ICT titer two weekly and MCA PSV two weekly. At 22 weeks titer increased to 1:128. Three doses of IVIG 1 gm/kg were given at weekly interval. At the end of third IVIG dose her ICT titer dropped

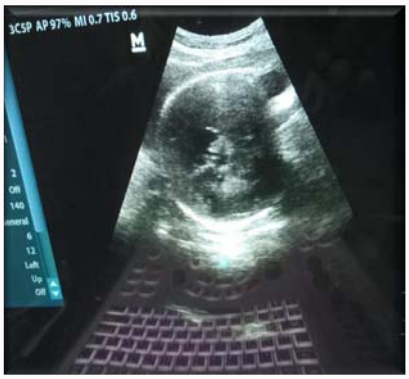

Figure 5: Resolved fetal scalp edema after multiple transfusion.

to 1:8. Subsequently she was monitored with ICT titer two weekly. When it became 1:32 at 30 weeks gestation she was monitored weekly with MCA PSV. Till 35 weeks MCA PSV was between 1 to 1.29 MoM and did not require any intrauterine transfusion. At 35 weeks 05 days she went in to spontaneous labor and emergency LSCS was done due to breech presentation and delivered a 2.2 kg female baby with positive blood group. Baby did not require exchange transfusion or IVIG infusion. Baby was only managed with phototherapy and discharged on 10th postnatal day.

IVIG in babies after birth

In one such scenario (case no 5) managed at our centre at 31 years old with 34 weeks gestation with ICT titer of 1:32 with cardiomegaly with MCA PSV of more than 1.5 MoM had no sign of hydrops on

sonography. Surfactant induction given to mother and baby delivered at 34 weeks 3 days with Hb of 8 gm% and serum bilirubin of 6 mg/dl. IV Ig two doses and phototherapy given to baby in NICU and observed without exchange transfusion. Patient was discharged on day 29 with Hb of 11 gm%.

Conclusion

Each Rh isoimmunized pregnancy should be offered ICT titer and when it is above the critical titer of 1:16, the patient should be monitored with MCA PSV after 16 weeks. When MCA PSV has become more than 1.5 MoM, she should be offered intrauterine transfusion. If MCA PSV is not raising above 1.5 MoM. Monitoring should be continued with MCA PSV and delivery should be advised at 36 to 37 weeks, if MCA PSV values are within normal range. Where ICT titer is very high in early pregnancy IVIG can be given to postpone intra uterine transfusion at a later gestation. At our hospital total three patients required intrauterine transfusion, three patients monitored with MCA PSV and without antenatal intervention and one patient was given three doses of IVIG antenatally.

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