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Original Article

Treatment of Fetal Anemia in Rh Isoimmunized pregnancies With Intrauterine Fetal Blood Transfusion

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Abstract

Introduction: Despite the availability of prophylactic rhesus immune globulin, hemolytic disease of the newborn and fetal death (hydrops fetalis) due to rhesus alloimmunization, is still a major contributor to perinatal morbidity and mortality in India. Pregnancy outcome after fetal therapy with ultrasound guided intrauterine transfusion (IUT) for fetal anemia was studied. *Methods:* A prospective cohort study of 99 Rh isoimmunized pregnancies, Indirect Coomb's test Positive (ICT > 1:16) was conducted from July 2002 to June 2007. Intensive fetal monitoring by serial ultrasound and middle cerebral artery peak systolic velocity using Color Doppler was performed to detect fetal anemia. When necessary, invasive testing with cordocentesis for Hb, PCV was performed if pregnancy was less than 32–34 weeks gestation. If PCV was <30, or there was fetal hydrops, Ultrasound guided intrauterine transfusion was carried out by the intravascular (IVT) or the intraperitoneal (IPT) routes. Primary outcome variables were fetal survival in relation to gestational age and procedure related factors. *Result:* Of 99 pregnancies, 43 cases (25 – hydropic, 18-nonhydropic fetuses) required 135 intrauterine blood transfusions. The rest 56 pregnancies were managed conservatively and did not need IUT. IUTs were performed when indicated starting from 16 weeks (IPT) and 21 weeks (IVT) of gestation by the intraperitoneal / intravascular routes respectively. Pre-transfusion Hb ranged from 3g% to 8g%. The amount of blood transfused varied from 10 ml to > 110 ml depending on the period of gestation and degree of fetal anemia. The number of transfusions per pregnancy was 1-7, at intervals of 1-4 weeks, till delivery at 28 to 36 weeks of gestation. Survival of hydropic babies (88%) was almost similar to those without hydrops (83.3%) Prognosis was slightly better in Rh isoimmunized pregnancies not requiring IUT (94%) compared to fetuses receiving transfusions (85.6%)*Conclusion:* Intrauterine fetal blood transfusion was found to be the only life saving therapy, and very effective in the management of preterm Rh isoimmunized pregnancies. Results are comparable with the best centers in the world, hence early referral to specialized centers with expertise of specialized intensive fetal monitoring for early diagnosis of fetal anemia, and of intrauterine fetal blood transfusion are important for optimal perinatal outcome.

Key words : Rh isoimmunsation, Intrauterine transfusion, fetus.

Introduction:

The discovery of Rhesus factor by Landsteiner in 1940[1] and the association of 'hydrops fetalis' with erythroblastosis fetalis led to the understanding of the pathogenesis and the complications of Rh sensitization. This is fetal / neonatal hemolytic disease leading to neonatal jaundice in the mild cases, to kernicterus and cerebral palsy, neonatal death, need for exchange transfusions, hydrops fetalis and finally intrauterine death in the severe cases. Prognosis in subsequent pregnancy is considered worse as fetal anemia sets in 8-10 weeks earlier than in previous pregnancy.

Introduction and utilization of Rh D immunoglobulin

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(Anti D) for prophylaxis against Rh immunization – initially postpartum and subsequently antepartum is one of the major medical achievements and successful application of preventive obstetric medicine in the last century. However in India, a major percentage of the women have home deliveries, and Rh grouping is not done; also because of the high cost of Anti –D or due to negligence, prophylaxis is not instituted. As a result, a large number of patients develop Rh isoimmunization and subsequent fetal losses, sometimes to the extent of three to ten hydropic babies before seeking advice from a tertiary care center.

Management options in severe Rh-isoimmunization have been very gloomy – and include termination of pregnancy, permanent sterilization or the highly controversial pregnancy with Rh negative donor semen. In most places including teaching hospitals, management is solely by preterm delivery and neonatal exchange transfusion as soon as the fetus is about 32 – 34 weeks of gestation. Historically, various techniques have been tried to correct fetal anemia in fetuses less than 32 weeks – cannulation of placental vessels at hysterotomy, plasmapheresis, fluoroscopic guided intraperitoneal transfusion, and fetoscopic guided intrauterine transfusion[2]. However it was the advent of Ultrasonography and U/S guided cord blood sampling that enabled the present state-of-the-art diagnosis and subsequently revolutionized the therapy of fetal anemia by direct U/S guided fetal blood transfusion[3].

Very few centers in India have the facility or have reported the management and prognosis of high risk pregnant patients with Rh isoimmunization using ultrasound guided intrauterine fetal blood transfusions.

Aim and objectives

To assess pregnancy outcome after prenatal treatment with ultrasound guided intrauterine fetal blood transfusion (IUT) for fetal anemia due to Rh isoimmunization.

Material and Methods

A prospective cohort study of ninety nine Rh isoimmunized pregnancies referred to the Fetal Medicine Unit at AIIMS was conducted from July 2002 to June 2007 (5 years)

Management Protocol: At booking, Indirect Coombs Test (ICT) was done, and positive (+ve) titer of more than 1:16 was considered critical level when the fetus is at risk of anemia. History of previous hydrops fetalis, immunized pregnancy, stillbirth or neonatal death was taken.

Fetal monitoring for early diagnosis of fetal anemia was done at regular intervals from 14–16 weeks onwards by serial ultrasound and middle cerebral artery peak systolic velocity using Color Doppler.

Ultrasound – for hepatomegaly, placentomegaly, cardiomegaly, polyhydramnios, hydrops – ascitis, pleural, pericardial effusions and scalp edema.

Middle Cerebral Artery Doppler Peak Systolic Velocity (MCA – PSV)[4] measurement procedure:

Axial section of brain, including thalami, cavita septi pellucidi was obtained and the Circle of Willis was identified. The middle cerebral artery (MCA) nearest to U/S probe was identified, Doppler ultrasound switched on and the peak systolic velocity measured carefully. Mari's normograms in MoM established for various gestational ages used.

Cordocentesis was performed if PSV- MoM = >1.5. Blood was collected for hemoglobin, hematocrit (in capillary tube), and blood group – ABO&Rh. Intrauterine transfusion (IUT) was carried out at the same sitting if fetal hemoglobin was less than 10gm% or hematocrit was less than 30. If there was fetal hydrops on ultrasound, the condition was categorized as severe fetal anemia requiring IUT.

Intrauterine transfusion (IUT) was performed by the following techniques:

Intra Vascular Transfusion (IVT). This route was tried first especially if the fetus was hydropic. Volume of blood transfused was quickly calculated after the first cord blood sampling for hemoglobin and hematocrit levels:

$$\frac{\text{donor hct} - \text{desired hct}}{\text{desired hct} - \text{fetal hct}} \times \text{feto} - \text{placental blood vol} \quad (150\text{ml/kg})$$

Intra Peritoneal Transfusion (IPT) If approach to cord was difficult (posterior placenta, obesity, early gestation) Volume transfused : POG (weeks) -20x10ml

Procedure – intrauterine fetal blood transfusion[5]: Ultrasound and Color Doppler was first done for fetal heart activity, and placental site. Access site and needle path were mapped with plan to enter the cord at cord insertion or free loop. Fetus was paralyzed using Vecuronium IM/IV 0.3mgm/kg fetal wt into fetal buttock or umbilical vein, if fetal movements were excessive or placenta was posterior. A 20 gauge long needle was inserted under continuous U/S guidance by free hand technique. Needle tip was inserted with a sharp jerk into the umbilical vein, (IVT) the stillete withdrawn, syringe attached and 2-3ml blood aspirated and sent for Hb, PCV, blood group. In IPT, needle was inserted into the fetal peritoneal cavity.

Packed 'O' –ve RBC (hct 75-80%) was then transfused by pushing the required volume with a 10/20cc syringe at the rate of about 10ml/min. After the transfusion in IVT, blood for post transfusion hematocrit was aspirated. Fetal heart activity was checked intermittently throughout the procedure for tachycardia, bradycardia or other complications.

Fetal Monitoring was subsequently carried out by ultrasound for anemia, and MCA-PSV measurements. Repeat transfusion time was calculated assuming a post transfusion hematocrit fall of 1% per day and by MCA-PSV measurements.

Fetal wellbeing was monitored by daily kick counts and biophysical profile.

Delivery by Cesarean section or by the vaginal route – depending on cervical assessment was considered after 34-36 weeks of gestation. Baby was cared for by neonatologists for anemia, jaundice and other problems such as prematurity, and managed by exchange transfusions etc. as required.

Results

There were 99 Rh isoimmunized pregnancies (July 2002 – June2007), of which 25 fetuses were hydropic at referral, and the remaining 74 were nonhydropic (Table I). In 56 cases, intensive monitoring did not reveal the need for fetal blood transfusion. However in 43 cases there was moderate to severe fetal anemia necessitating intrauterine fetal blood transfusion (IUT). IUT was performed 135 times in these 43 cases. Most of the patients had a history of affected pregnancies (Table- II).

In majority of the cases IUT was performed at 24–31 weeks, though in several cases fetuses received blood

Table I

Showing number of hydropic / non-hydropic fetuses at presentation

Rh isoimmunized pregnancies -99	
Hydropic at presentation	– 25
Non hydropic	– 74
· Intensive monitoring only	– 56 cases
· **Intrauterine transfusion performed**	**- 43 cases - 135 times**

Table II

Previous obstetric history (99 Cases)

	Still births		Neonatal deaths		MTPs for Rh isoimmunization	h/o IUTs
	Hydropic fetuses	Non-hydropic fetuses	Hydropic fetuses	Non-hydropic fetuses		
1	3	2	2	1	3	2
2	5	2	2	1	2	1
3	4	3	1	2		
4	2	1	3	1		
≥5	4	2	1	1		

as early as 16–18 weeks and as late as >32 weeks of pregnancy (Table – III). The amount of blood transfused ranged from 10 - >110 ml, depending on the calculation based on fetal age, presence of hydrops and cord blood hematocrit (Table IV). IUT had to be repeated at regular intervals till the fetuses reached 34–36 weeks in 80% of the patients, some requiring as many as 3–7 transfusions during the course of one pregnancy (Table V).

Intrauterine transfusion enabled pregnancies to be carried on successfully to 31–32 weeks in 70% of the cases, and beyond 34-36 weeks in 30% of the cases (Table VI).

Severe persistent bradycardia occurred during the procedure in two cases necessitating emergency Cesarean section, of which cord hematoma was found in one patient. Premature rupture of membranes occurred in five cases and preterm labor in 13 patients.

Mode of delivery was by elective Cesarean section (CS) in only 14 (32.5%) cases and by emergency CS in 15 (35%) cases. Due to favorable cervix in multiparous women, vaginal delivery with intrapartum electronic monitoring was allowed successfully in 14 (32.5%) women who had received intrauterine fetal blood transfusions (Table VII).

Fetal and neonatal outcome (Table-VIII) – in the 25 hydropic fetuses showed that there were two intrauterine deaths and one neonatal death, with 22 (88%) live babies at discharge. In the 18 non-hydropic fetuses who received IUT there were two intrauterine deaths, and one neonatal death, with a survival rate of 83.3%.

In the non-hydropic (56 cases) fetuses that were managed by fetal monitoring alone without IUT, there were two intrauterine, and one neonatal death due to non–Rh related conditions (hypertension and growth restriction), survival being 94%.

Table III
Period of Gestation at IUT

POG	IVT	IPT	IVT+IPT	Total
16-18W		1		1
19-21W	1	2	1	4
22-23W	4	14		18
24-25W	17	4	4	25
26-27W	23	2	1	26
28-29W	21		7	28
30-31W	23		1	24
>32W	8		1	9
Total	97	23	15	135

Table IV
Amount of blood transfused at I.U.T

10-30 ml	11
31-50ml	39
51-70ml	37
71-90ml	32
91-110ml	12
>110ml	04
Total:	(43 Cases) 135 times

Table V
Number of IUTs per pregnancy

No. of UTs/case	No. of cases (43)
1	8
2	8
3	12
4	7
5	2
6	4
7	2

Table VI
Period of Gestation at delivery

IUT(56)	IUT(43)	Non
<28 weeks	2	-
29-30 weeks	11	3
31-32 weeks	17	6
33-34 weeks	10	8
35-36 weeks	3	21
37-38 weeks	-	15
40 weeks	-	3

Table VII
Mode of delivery

Elective CS-	14 (32.5%)
Emergency CS-	15 (35%)
Vaginal delivery	14 (32.5%)

Table VIII
Fetal Outcome

1. IUT performed (43 cases, 135 times)	
Hydropic fetuses (25 cases)	
Intrauterine deaths	02
Neonatal death	01
Live babies	22 (88%)
Non-hydropic fetuses (18 cases)	
Intrauterine death	2
Neonatal death	1
Live babies	15 (83.3%)
2. Non-IUT non-hydropic (56 cases)	
Intrauterine death	2
Neonatal death	1
Live babies	53 (94%)

Discussion

Management of fetal anemia is not possible without ultrasound monitoring and U/S guided intrauterine fetal blood transfusion. It is however a very difficult procedure requiring a lot of skill and precision, with a considerably high rate of procedure related fetal deaths[7]. A variety of techniques such as exchange, partial exchange or simple top–up transfusion via different sites such as percutaneous umbilical cord puncture at placental insertion site or free loop, the intrahepatic umbilical vein or intraperitoneal transfusion have been employed.

In 44 ultrasound guided intravascular transfusions performed between 18 and 32 weeks on 15 patients with severe erythroblastosis fetalis due to Rh immunization, five transfusions were done in the intrahepatic umbilical vein, six were simple transfusions via percutaneous umbilical cord puncture, and 33 were partial exchange[8]. The overall survival rate was 67% (10 of 15 cases): 4 of the 8 hydropic fetuses (50%) and 6 of the 7 nonhydropic fetuses (83%) were alive at birth and survived the perinatal period. Three of the five losses occurred among the first four cases, while in the last 11 cases the survival rate increased to 82% (9 of 11).

In another series, of ultrasound guided fetal intravascular transfusions in 78 fetuses, at the Royal Women's Hospital all with severe erythroblastosis, a total of 288 intrauterine transfusions were attempted with an overall survival rate of 75.6% (59 of 78)[9]. The overall survival rate for delivered fetuses improved from 64.3% (18 of 28) in 1984–1987, to 82% (41 of 50) in 1988–1993. There was a total of 33 hydropic fetuses, of whom 20 (60.6%) survived, significantly fewer compared with 86.7% (39 of 45) of the nonhydropic fetuses (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.09 to 0.70, p <. 01). Fetuses who were more sick at the time of transfusion, as reflected by larger hemoglobin deficits, had lower survival rates, as did those requiring transfusions at earlier gestational ages. When these variables were allowed for, the survival rate significantly improves over time (OR 6.3, 95% CI 1.3 to 30.4, $p<0.05$). This was probably reflecting the increased skill of the operators, as it was in our series where the surviving babies were actually more in the hydropic fetus group (88% vs 83.3%). The presence of hydrops per se was not considered important. Variations of the technique employed, such as exchange or intraperitoneal transfusion, or different sites for transfusion, were not significantly related to survival.

Intravascular transfusion is now believed to be a more precise method for treating fetal anemia in erythroblastosis fetalis than is intraperitoneal transfusion. Previously established guidelines for the volume of blood to be given in intravascular transfusion at a specific gestational age are not applicable for intravascular transfusion. In 28 patients, intravascular transfusion was performed on 81 occasions between 19-34 weeks gestation[10]. The total number of transfusions ranged from one to six per patient. The aim at each procedure was to achieve a final hematocrit of 35-50%. Factors that determined the volume of blood required included pretransfusion hematocrit, post – minus pre – transfusion hematocrit (hematocrit increase), the hematocrit of the transfused blood, gestational age, estimated fetal weight and interval from last transfusion. Intravascular as opposed to intraperitoneal transfusions were found to be the main method of transfusion in the later years in this study, a finding which was expected with improved

sonographic equipment. Apart from this, management and prognosis of anti-D red cell isoimmunization in pregnancy was found to have remained relatively stable since the 1980s.

Very few centers in India are performing IUTs. One study from Mumbai[11] reported 67 intrauterine transfusions (IUT) carried out for 27 cases. Mean gestation age at first IUT was 27+/-2.9 weeks. Of the 11 fetuses having gross ascites, eight were stillborn and two non-hydropic fetuses died. Two neonates died due to hemorrhagic disorder and prematurity, resulting in an overall survival rate of 55.6%. Late referrals, severe Rh alloimmunization, volume overload, delay in IUT because of non availability of blood were thought to be reasons for the poor outcome.

Conclusions

In our experience, intrauterine fetal blood transfusion was found to be life saving, and very effective in the management of preterm Rh isoimmunized pregnancies. The results are comparable with the best centers in the world[12,13]. Early referral to specialized centers with expertise of intensive fetal monitoring for early diagnosis of fetal anemia, and of intrauterine fetal blood transfusion are most important for optimal perinatal outcome[14].

References

1. Hajdu SI. Blood transfusion from antiquity to the discovery of the Rh factor. *Ann Clin Lab Sci 2003:33:471-3.*
2. Rodeck CH, Nicolaides KH, Warsof SL, et al. The management of severe rhesus isoimmunization by fetoscopic intravascular transfusions. *Am J Obstet Gynecol 1984;150:769-74*.
3. Brennand J, Cameron A. Fetal anemia: diagnosis and management. *Best Pract Res Clin Obstet Gynaecol. 2008;22:15-29*
4. Mari G, Deter RL, Carpenter RL et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood velocity in Anemic Fetuses. *N Engl J Med 2000;342:9-14*.
5. Kanhai HH, Bennebroek Gravenhorst J, van Kamp IL et al. Management of severe hemolytic disease with ultrasound guided intravascular fetal transfusions. *Vox Sang 1990;59:180-4*.
6. Howe DT, Michailidis GD. Intraperitoneal transfusion in severe, early-onset Rh isoimmunization. *Obstet Gynecol 2007;110: 880-4*.
7. Van Kamp IL, Klumper FJ, Meerman RH et al. Treatment of fetal anemia due to red-cell alloimmunization with intrauterine transfusions in the Netherlands, 1988-1999. *Acta Obstet Gynecol Scand 2004;83:731-7*.
8. Orsini et al. Intravascular intrauterine transfusion for severe erythroblastosis fetalis using different techniques. *Fetal Ther 1988;3:50-9*.
9. Sampson AJ, Permezel M, Doyle LW et al. Ultrasound guided fetal intravascular transfusions for severe erythroblastosis 1984-1993. *Aust N Z J Obstet Gynaecol 1994;34:125-30*.
10. Cheong YC, Goodrick J, Kyle PM et al. Management of anti-Rhesus-antibodies in pregnancy: a review from 1994 to 1998. *Fetal Diagn Ther 2001;16:294-8*.
11. Gupte SC, Lulla CP, Kulkarni SS et al. Experience with intrauterine transfusions for severe Rh alloimmunization in a developing country. *J Matern Fetal Med 1998;7:287-91*.
12. Van Kamp IL, Klumper FJ, Oepkes D et al. Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. *Am J Obstet Gynecol 2005;192:171-7*.
13. Oepkes D, Adama van Scheltema P. Intrauterine fetal transfusions in the management of fetal anemia and fetal thrombocytopenia. *Semin Fetal Neonatal Med 2007;12: 432-8*.
14. De Boer IP, Zeestraten EC, Lopriore E et al. Pediatric outcome in Rhesus hemolytic disease treated with and without intrauterine transfusion. *Am J Obstet Gynecol 2008;198:54.*