The Journal of Obstetrics and Gynecology of India (November–December 2021) 71(6):583–590
https://doi.org/10.1007/s13224-021-01455-4

ORIGINAL ARTICLE

Pregnancy Outcome of Rh D Alloimmunized Pregnancies: A Tertiary Care Institute Experience of a Developing Country

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Received: 7 July 2020 / Accepted: 28 January 2021 / Published online: 21 July 2021

Abstract

Aim To determine the socio-demographic characteristics and pregnancy outcome of Rh D alloimmunized women monitored with MCA PSV (middle cerebral artery peak systolic velocity).

Materials and Methods In total, 363 Rh D alloimmunized women attended antenatal clinic or obstetric emergency between January 2006 and December 2014. MCA PSV was the screening method for detection of fetal anemia. Intrauterine blood transfusion (IUT) was given when MCA PSV was > 1.5 MOM. Totally, 162 women (164 fetuses) received 492 transfusions. Forty-eight women had fetal hydrops at presentation. Five women (three received IUT) were lost to follow-up. Pregnancy outcome of 358 women and socio-demographic characteristics of 363 women were analyzed.

Results The perinatal mortality was 421, 66 and 87 per 1000 live births in hydrops group, non-hydrops IUT group and non-IUT group, respectively.

Conclusion Rh alloimmunization is still a major cause of perinatal morbidity and mortality. The higher gravidity, previous history of pregnancy wastage, still births and hydrops increase the requirement of intrauterine transfusion. MCA PSV is an excellent tool for monitoring of Rh alloimmunized pregnancies to detect fetal anemia. Early detection and monitoring by MCA PSV improve its outcome.

Keywords Rh D · Alloimmunization · MCA PSV · Intrauterine transfusion · Hydrops

Introduction

Use of Rh D antibody antenatally and postnatally in Rh D-negative non-immunized women as per guidelines has substantially decreased the incidence of Rh D alloimmunization, particularly in the developed countries [1]. In India, however, Rh D alloimmunization is still a major problem. A recent hospital-based study among multigravida women attending antenatal clinics showed the prevalence of erythrocyte alloantibodies to be 1.25%, while Rh D contributed to 78% of them. Alloimmunization rate among Rh D-negative women was 10.4%. Adverse pregnancy outcome was 10 times higher among these women [2].

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PGIMER, Chandigarh, being tertiary care center, caters to management of Rh D alloimmunized pregnant women living in the northern part of India. In 2006, management program incorporated middle cerebral artery peak systolic velocity (MCA PSV) as a standard of care for monitoring fetal anemia. Only few large studies have reported outcome of Rh alloimmunized women monitored solely with MCA PSV. The aim of this study was to find out the socio-demographic characteristics and pregnancy outcome of Rh D alloimmunized women monitored with MCA PSV.

Material and Methods

This was retrospective observational study. Institute Ethics Committee approval was taken. Indirect Coombs' test (ICT) was done to detect irregular antibodies in all Rh D-negative pregnant women attending antenatal clinic of PGIMER, Chandigarh, between January 2006 and December 2014. Subsequently, antibody screen (3 cell panel, ID-Diapanel, Bio-Rad Switzerland) to determine the antibody specificity was done. These tests were performed using column agglutination (gel) technique (LISS Coombs AHG card, Bio-Rad Switzerland). Estimation of anti-D alloantibody was done by tube titration method, where serial doubling dilutions of patient's serum were prepared and tested till antihuman globulin (AHG) phase after incubation of all the tubes at 37 °C for 45 min followed by centrifugation and three times washing with saline and finally addition of polyspecific AHG (anti IgG + anti-C3d) antisera (Tulip Diagnostics Ltd., Goa, India). Appropriate controls (positive and negative) were used to validate the test. The titre was reported as highest dilution at which agglutination was observed. Anti-D titre ≥ 1:16 was considered as critical titre. MCA PSV monitoring was initiated earliest at 16–18 weeks of gestation in women who had past obstetric history suggesting hemolytic disease of fetus or new born (HDFN) or had ICT titre ≥ 1:16. In the presence of hydrops, MCA PSV measurement was carried out even in the absence of titre.

MCA PSV measurements were performed as has been described by Mari G et al. [3]. Angle correction software was not used. If required, repeat examinations were carried out to have insonation angle between 0 and 15°.

In case of consistently high MCA PSV > 1.5MOM, fetal blood sampling was performed; hematocrit, hemoglobin and blood group were determined and blood transfusion was given if hematocrit was 30% or less. Intravascular access was via cord vein near placental insertion or intra-hepatic portion of umbilical vein when cord insertion site was not accessible. Free cord loop was the last choice. Rarely, intraperitoneal transfusion was given as combined or sole mode when intravascular transfusion was not possible. Freshly stored (3–5 days of collection) O negative packed red blood cells (PRBCs) with 70–75% hematocrit, irradiated, compatible with mother were used for transfusion. In addition, PRBC was extended phenotype matched with mother for extended Rh C, E and c antigens, and also for any other antigen against which the alloimmunized mother has developed alloantibody. Amount of blood to be transfused was determined from the estimated fetal weight and pre-transfusion hematocrit using formula of Giannia G et al. [4]. Target PCV was 45%.

Second and subsequent transfusion was planned when estimated hematocrit was less than 30%, calculating 1% reduction in hematocrit per day from post-transfusion hematocrit. In case MCA PSV was consistently lower than 1.5 MOM for the gestation, intrauterine transfusion (IUT) was delayed. Delivery was planned at or beyond 36 weeks of gestation.

Neonatal hematocrit, total serum bilirubin, reticulocyte count, blood group and direct Coombs test were determined at birth. Management of neonates included exchange transfusion (ET), phototherapy (PT) and intravenous immunoglobulins (IVIg) as per assessment by neonatologists. Pregnancy outcome in relation to need for IUT and presence or absence of hydrops were studied. Discharge of neonates in a satisfactory condition, abortion, intrauterine fetal death (IUFD) or neonatal death were outcome measures. Fetal or neonatal complications were ascribed to IUT when those occurred within one week of IUT and no other cause was obvious. Abortion was defined as pregnancy wastage before 26 weeks of gestation.

Discrete categorical data were represented in the form of either number or percentage (%). For normally distributed data, means of three groups were compared using one-way ANOVA followed by post hoc multiple comparisons test. For skewed data, Kruskal–Wallis test followed by Mann–Whitney test for two groups was applied. For normally distributed data, two groups were compared by Student's t test. Chi-squared test or Fisher's exact test whichever was appropriate was applied for categorical data. All the statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Analysis was conducted using IBM SPSS Statistics (version 22.0).

Results

During the study period, 44,145 women delivered, of which 2334 (5.28%) women were Rh D negative. Three hundred sixty-three women (15.55%) were alloimmunized with anti-D alloantibody. This cohort included 8 women with twin pregnancies and 48 women (13.2%) with hydrops. None of our patients developed hydrops while monitoring. Severe anemia was missed in one fetus which was diagnosed at birth. One hundred and sixty-two (44.6%) women which

included two twin pregnancies, i.e., 164 fetuses, received 492 IUTs. Five women with singleton pregnancies (three received IUT) were lost to follow-up. Their delivery details and perinatal outcomes were not known; hence, these patients were excluded from analysis of pregnancy outcome (Fig. 1). Their demographic data, however, were analyzed.

The demographic characteristics of women who did not require IUT were compared with those who required IUT (Table 1). In this cohort, mean age was 28.8 ± 3.7 years and mean gravida was 4.09. Gravidity ≥ 5 (p 0.000), previous pregnancy wastage ≥ 4 (p 0.000), previous history of cesarean section ($p = 0.026$), stillbirth ($p = 0.000$) and hydrops (0.000) were significantly more common in women who required IUT. The history of antepartum hemorrhage, postpartum hemorrhage, neonatal jaundice and blood transfusion in previous pregnancies were not different between the groups. Approximately 22% women did not receive any form of anti-D immuno-prophylaxis in the past, whereas 31% received only postpartum or post-abortal prophylaxis after each pregnancy event. 4.68% alloimmunized women were immunized in their first pregnancy (Table 1).

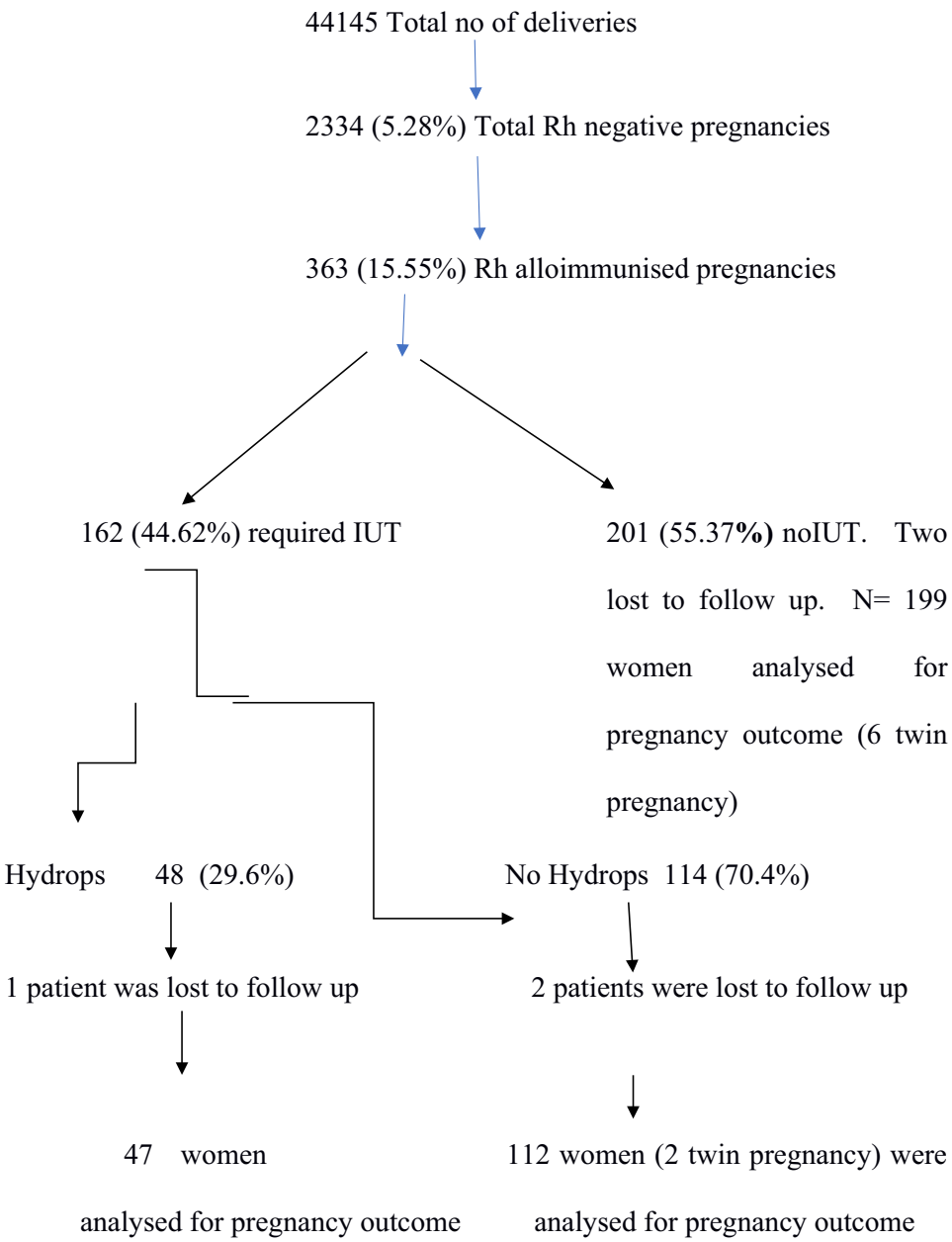

Figure1 Flow diagram of the cohort

Table 1 Demographic characteristics of all women treated

	Required IUT		No IUT required $N=201$ (%)	*P* value
	With hydrops $N=48$(%)	Without hydrops $N=114$(%)		
Age mean ± SD	29.6 ± 3	29 ± 3.9	28.4 ± 3.7	
Mean gravidity	4.7	4.9	3.5	
Previous pregnancy wastage mean ± SD and median	2.8 ± 1.4 3.00	2.9 ± 2 3.00	1.4 ± 1.3 1.00	*p*.000
Booking gestation mean ± SD	24.9 ± 5.8	22.4 ± 7.47	26.14 ± 8.64	*p*.000
Past H/O hydrops	19 (39.58)	36 (31.6)	10 (4.97)	*p*.000
Neonatal jaundice in previous pregnancies	13 (27.08)	36 (31.6)	50 (24.87)	*p*.424
Stillbirths in past	31 (64.58)	58 (50.9)	34 (16.92)	*p*.000
Anti-D prophylaxis in previous pregnancies				
Received in one or more pregnancies	22 (45.83%)	60 (52.6%)	70 (34.82%)	*p*.0094
Received in all pregnancies	16 (33.33%)	32 (28.1%)	65 (32.33%)	*p*.6737
Not received in any pregnancy	10 (20.83%)	22 (19.3%)	49 (24.37%)	*p*.5857
Immunized in first pregnancy	0	0	17 (8.45%)	*p*.0008

All women had anti-D alloantibodies either alone or in combination with other alloantibodies (Table 2)**.** Multiple antibodies were more common (26.1% vs. 14%) in women who needed IUT indicating that the presence of multiple antibodies increases the severity of fetal affection.

Approximately 74% of women who received IUT as compared to 38% who did not had anti D titre of ≥ 1:64 at the time of booking (*p* 0.000). Five women (3%) received IUT even when baseline anti-D titre was below critical titre of 1:16 underscoring the need for close monitoring in all cases of Rh D alloimmunized pregnancies. One of these patients had anti-D titre of 1:1 and underwent CVS for thalassemia at 11 weeks following which her titre increased to 1:128. Rest of 4 women had bad obstetric history with history of stillbirth of unknown reason in two cases.

The lowest gestation at first IUT was 19.5 weeks, and the highest gestation was 35 weeks. Median number of IUT was 3, and the number of IUTs ranged from 1 to 7. Thirty patients had received single IUT.

The most common route of IUT was cord vein (65%). Intraperitoneal transfusion was required in 2 patients either alone or in combination with intra-hepatic route due to difficult vascular access at 22–24 weeks of gestation.

The mean PCV at first IUT was 13.37 ± 7.28% in hydropic fetuses and 21.71 ± 7.38% in non-hydropic fetuses.

IUT-related serious complications were seen in approximately 3.8% of procedures. The complications of IUT included IUFD (1.6%), severe bradycardia requiring immediate delivery (1%), abortions (0.6%), preterm premature

Table 2 Type of antibodies present and ICT titre

	Hydrops requiring IUT ($n=48$)	IUT non-hydrops requiring IUT ($N=114$)	Non-IUT group ($n=201$)	*P* value
Alloantibody status				
D	30(62.5%)	89 (78.07)	172(85.57)	
D,C	13(27.08)	20 (17.54)	22(10.94)	
CDE	0	3(2.63)	4(1.99)	
Others	5(10.41)	2(1.75)	3(1.49)	
ICT Titre at booking	IUT hydrops group ($n=48$)	IUT non-hydrops group ($N=114$)	Non-IUT group ($n=201$)	
≥256	18 (37.5)	24 (21.05)	20 (9.95)	p .0001
64 – 128	23 (47.91)	56 (49.12)	46 (22.88)	p .0002
16 – 32	6 (12.5)	30 (26.31)	46 (22.88)	p .1738
4–8	1 (2.08)	2 (1.75)	56 (27.86)	p .0001
1–2	0	2 (1.75)	32 (15.92)	p .0001
Multiple antibodies	0	0	1 (0.49)	

rupture of membranes (0.2%) and fever (0.4%). Transient bradycardia was seen during 4.1% of the procedures.

The mean gestation, mode of delivery and pregnancy outcome are given in Table 3. Fifty percent of women in IUT hydrops (IH) group whereas 27.3% and 18.8% in non-hydrops IUT (NHI) group and non-IUT (NI) group, respectively, delivered at ≤ 34 weeks of gestation (Table 3). Preterm delivery was a significant problem in those who required IUT particularly in the presence of hydrops. Forty-five percent of women in the entire cohort underwent planned or unplanned cesarean section (CS). CS rate was higher in IUT than in non-IUT group (p 0.001). CS rate was comparatively lower in hydrops group because of higher rate of IUFD and poor survival chance in the neonatal period (Table 3).

The perinatal mortality was very high (421 per 1000 live births) in IH, whereas it was 66 and 87, respectively, in NHI and NI group. The various causes of perinatal mortality are highlighted in Table 3.

Statistically significantly higher number of neonates (34.2%, $p = 0.001$) in IH had 1-min APGAR score of less than 7 (Table 4). Among hydropic fetuses, 20.5% had very low birth weight less than 1.5 kg, whereas only 6.36% in NHI group and 9.74% in NI group were below 1.5 kg. Neonatal management modalities used in different groups are shown in Table 4.

Discussion

The incidence of hemolytic disease of fetus and newborn (HDFN) has drastically reduced in developed countries after the introduction of Rh D immuno-prophylaxis [1].

In the absence of immuno-prophylaxis, 14% of Rh D-negative women will develop anti-D antibody. Alloimmunization rate reduces to 1.8–2% with postpartum prophylaxis.

Table 3 Pregnancy outcome and gestation at delivery

	Hydrops required IUT $N=47$	Non hydrops required IUT $N=112$	No IUT required $N=199$
Twin pregnancy	0	2	6
Abortion	3	4	3
Gestation at delivery (weeks) mean ± SD	32.59 ± 3.64	34.22 ± 3.03	35.80 ± 3.13
	$N=44$	$N=110$	$N=202$
LSCS	16 (36.36%)	74 (67.27%)	74 (36.63%)
Vaginal delivery	28 (63.63%)	36 (32.72%)	128 (63.36%)
Perinatal outcome	$N=44$ (%)	$N=110$ (%)	$N=202$ (%)
Neonatal death	10 (22.72) Sepsis—2 CHF—2 Prematurity—2 Abruption—1 Birth Asphyxia—2 Multiorgan failure—1	3 (2.72) Sepsis—3	10 (4.95) Sepsis—6 Severe anemia—1 Rupture uterus—1 Prematurity—2
Still birth	6 (13.63) IUT related—4 Abruption—1 Unknown—1	4 (3.63) IUT related—2 CMF—1 Unknown—1	7 (3.46) IUGR—3 Abruption—3 Unknown—1
Discharged home in satisfactory condition	28 (63.63%)	103 (93.63%)	185 (91.58%)
Perinatal mortality/1000 live births	421	66	87
Gestation at delivery (weeks)	IUT hydrops group $N=44$	IUT non-hydrops group $N=110$	No IUT group $N=202$
26–30	9(20.45)	4(3.63)	9(4.45)
30 + 1–34	13(29.54)	26(23.63)	29(14.35)
34 + 1–36	17(38.63)	62 (56.36)	55(27.22)
> 36	5(11.36)	18(16.36)	109(53.96)
Mean ± SD	32.59 ± 3.64	34.22 ± 3.03	35.80 ± 3.13
P value	IUT hydrops versus IUT non-hydrops .011	IUT hydrops versus non-IUT .000	IUT non-hydrops versus non-IUT .000

Table 4 Neonatal weight, Apgar score and management

	Hydrops requiring IUT $n=38$ (%)	Non-hydrops requiring IUT $n=106$ (%)	No IUT $n=195$ (%)
APGAR < 7 min	13 (34.2)	11 (10.37)	15 (7.7)
Weight (Kg)	Hydrops $n=44$ (%)	Non-hydrops $n=110$ (%)	Non-IUT group $n=202$ (%)
≤ 1	4 (9.09)	2 (1.81)	11 (5.44)
1.01–1.49	5 (11.36)	5 (4.54)	8 (3.96)
1.5–1.99	11 (25)	21 (19.09)	25 (12.37)
2.0–2.49	12 (27.27)	41 (37.27)	52 (25.74)
2.50–2.99	12 (27.27)	36 (32.72)	73 (36.13)
3.00–3.49	0	5 (4.54)	24 (11.88)
≥ 3.5	0	0	9 (4.45)
Management	Hydrops requiring IUT $n=38$ (%)	Non-hydrops requiring IUT $n=106$(%)	Non-IUT group $n=195$ (%)
Exchange transfusion	26 (68.4)	83 (78.30)	72 (36.9)
Phototherapy	29 (76.3)	95 (89.62)	145 (74.4)
Intravenous immunoglobulins	18 (47.4)	61 (57.54)	82 (42.1)

Added antenatal prophylaxis further reduces the alloimmunization rate to 0.1–0.2% [1].

In India, there is no direct information from population-based study regarding extent of the problem of Rh D alloimmunization. A recent study calculated the number of pregnant women likely to develop Rh D alloimmunization in India from the prevalence of Rh negativity, estimated number of pregnant women at risk and units of Rh D immunoglobulin utilized [5].

Nearly 1.3 million Rh D-negative women were estimated to be pregnant annually, and nearly 1 million of them were estimated to be at risk. Eight lakh women would not receive prophylaxis; thus, one lakh women were estimated to develop alloimmunization annually [5].

In our study, 15.5% of Rh D-negative women were alloimmunized. Our hospital being a tertiary referral center, this figure might be an overestimate of the true prevalence.

Worrying fact is that 64% of the cohort did not receive even postpartum or post-abortal prophylaxis adequately. Thirty-one percent of women developed Rh D alloimmunization despite standard postpartum or post-abortal prophylaxis.

Ignorance about significance of Rh D immuno-prophylaxis at the levels of pregnant women as well as among their caregivers stands out to be a major problem of antenatal care delivery system. Other factors involved could be related to inadequate dose, suboptimal preparation or antenatal sensitization [6].

Rh alloimmunization in primigravidae is uncommon though can be explained by grandmother theory or by significant fetomaternal hemorrhage early in pregnancy. In our study, 4.68% of Rh alloimmunized women were primigravidae. Al Joudi et al. [7] in their study found 1.7% primigravidae to become immunized at the end of pregnancy.

The rate of Rh D alloimmunization increases with an increase in the number of pregnancies, being 4.9% after second and 45% after fifth pregnancy [7]. In our study, mean parity was 1.4 in NI group, whereas it was 2.8 and 2.9 in IH and NHI. This can be explained by the fact that with successive pregnancies, fetal antigens enhance antibody response in the mother which increased the severity. Also, women with severe alloimmunization were more likely to have higher number of pregnancy losses. In our study, significantly higher number of women who required IUT had past history of still births (Table 1).

MCA PSV monitoring by color Doppler ultrasonography is the standard method to look for fetal anemia. Sensitivity of this test to detect moderate to severe fetal anemia was 100% with a false positive rate of 12% [3]. A multicentric study found MCA PSV measurement to be more sensitive and accurate than amniocentesis [8]; however, sensitivity was not 100%. In another longitudinal study too, sensitivity of MCA PSV before 35 weeks was 88% and specificity was 87%. Two cases of moderate to severe anemia were missed. In both cases, interval between delivery and MCA PSV measurement was more than 2 weeks [9]. In our study, severe anemia was missed in one monitored fetus resulting in neonatal death, where last measurement was taken 2 weeks prior to delivery. Currently, we are repeating MCA PSV measurements every week particularly in third trimester.

Whether replacing amniocentesis with MCA PSV improves the pregnancy outcome has been studied [10, 11]. The number of live births was higher (80% vs. 95%), and the

Table 5 Pregnancy outcome according to gestation at first IUT

Gestation weeks	Fetus	D/S in a satisfactory condition (%)	Neonatal death	Stillbirth	Abortions
≤20 *n* = 4	Hydrops	1 (100)	0	0	0
	Non-hydrops	2 (66.7)	0	1	0
20.1–24 *n* = 34 (%)	Hydrops	7 (58.3)	1	1	3
	Non-hydrops	15 (68.2)	2	1	4
24.1–28 *n* = 45 (%)	Hydrops	12 (70.5)	2	3	0
	Non-hydrops	26 (92.9)	1	1	0
28.1–32 *n* = 44 (%)	hydrops	7 (53.8)	4	2	0
	Non-hydrops	30 (96.8)	0	1	0
32.1–35 *n* = 34 (%)	Hydrops	1 (25)	3	0	0
	Non-hydrops	30 (100)	0	0	0

need for ET in neonates was lower (80% vs. 33%) with introduction of MCA PSV monitoring in a small retrospective study [10]**.** In another retrospective study, impact of MCA PSV on neonatal outcome in alloimmunized pregnancies requiring IUT was evaluated [11]. Hydrops occurred more frequently during follow-up when pregnancies were monitored with amniocentesis (12% vs. 0%) than MCA PSV. Neonatal survival was better with MCA PSV-monitored group (100% vs. 86.5%) [11].

In a large cohort study spanning over 10 years, pregnancy outcome after IUT for fetal anemia due to RBC alloimmunization was studied. Overall neonatal survival was 86%. In the presence of hydrops, it was 78%, and in its absence, it was 92% [12]. In our study with IUT, 90% of fetuses were salvaged in the absence of hydrops, whereas in the presence of hydrops, it dropped to 59.5%. In non-IUT non-hydrops group, survival rate was 90%.

Dadhwal et al. [6] published their experience of treating 99 Rh D immunized women monitored with MCA PSV. Forty-three fetuses which included 25 hydropic fetuses required IUT. Eighty-eight percent of hydropic fetuses and 83% of non-hydropic fetuses survived [6].

Lower rate of survival in hydropic fetuses in our study probably was related to more severe degree of hydrops at presentation. In the absence of hydrops, perinatal survival steadily improved as the gestation increases at first IUT. Hydropic fetuses had poorer survival when first IUT was given later in gestation (Table 5). Poor neonatal condition at birth, extreme prematurity < 32 weeks and early preterm deliveries ≤ 34 weeks were more frequent in the presence of hydrops. Severity of hydrops has been related to poorer outcome in other studies too [13].

Intrauterine transfusion is a relatively safe procedure in expert hands. In a large retrospective cohort study, complications like fetal death, neonatal death, procedure-related infection and preterm premature rupture of membranes were found in 3.1% of procedures. Procedure-related pregnancy loss was 1.6% per procedure [14]. In a study by Pasman SA et al. [15], severe adverse effects were seen in 1.5% and mild in 10% of IUTs. They also found that IUT in free loop and hydrops were associated with more adverse events. In our study, procedure-related serious complications like IUFD, abortion, severe fetal bradycardia requiring delivery or preterm delivery occurred after 3.8% of procedures. Procedure-related fetal losses were higher in the presence of hydrops.

Rh D alloimmunization-related neonatal hyperbilirubinemia and related mortality and morbidity is still a major problem in lesser developed countries with higher neonatal mortality rate [16].

Even after treatment with intrauterine transfusions, 68% and 79% of neonates with or without hydrops required ET in our study. Even where IUT was not needed, 37% of neonates required exchange transfusions.

Conclusion

This study shows that Rh D alloimmunization-related perinatal morbidity and mortality is still a significant and less recognized problem in India. Intensive, skilled and costly treatment both during pregnancy and after delivery is required for its management to improve perinatal outcome.

Funding None.

Compliance with ethical standards

Conflict of interest There is no conflict of interest in connection with this article.

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