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ORIGINAL ARTICLE

Our Experience of Immune Fetal Hydrops: its Clinical Characteristics and Perinatal Outcome

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Abstract

Introduction Fetal hydrops is a serious condition which has high morbidity and mortality. Incidences of immune hydrops have decreased by manifold after introduction of anti-D immunoglobulin. Intra-uterine fetal blood transfusion revolutionized the treatment of these affected fetuses after diagnosis of immune fetal hydrops. In this study we aim to evaluate the clinical characteristics of immune hydropic fetuses and perinatal outcome after institution of intra-uterine transfusions.

Materials and methods A retrospective study was carried out in pregnant women with immune fetal hydrops from October 2004 to December 2019 in our tertiary care hospital. After diagnosis of fetal hydrops, all the fetuses received intra-uterine transfusions. All the newborns were followed up till 3 months postdelivery. All the fetuses were divided in two groups: hydrops diagnosed below 32 weeks (Group A) and in second group hydrops diagnosed after 32 weeks gestation (Group B).

Results Total 63 patients were diagnosed to have hydrops during the study period. Group A had 48 fetuses and Group B had 15 fetuses. Average gestational age of diagnosis of hydrops in group A was 24.2 weeks and in group B it was 32.5 weeks. All the fetuses received intra-vascular intra-uterine transfusion. Pericardial effusion was found to be significantly associated with group A. Successful perinatal outcome was seen in 92% fetuses. 87% fetuses had complete resolution of hydrops before delivery. All the fetuses received phototherapy and intra-venous immunoglobulin after delivery, and 5 fetuses underwent exchange transfusion.

Conclusion Favourable perinatal outcome was achieved in hydropic fetuses with intra-uterine blood transfusions. Complete resolution of hydrops before delivery increases the chances of perinatal survival.

Keywords Hydrops · Anti-D · Intra-uterine transfusion · Pericardial effusion · Middle cerebral artery-peak systolic velocity (MCA-PSV) · Intravenous immunoglobulin

Introduction

Haemolytic disease of fetus and newborn (HDFN) is one of the serious complication of pregnancy which has high incidence of perinatal mortality. Most commonly immune hydrops is caused by maternal red cell alloimmunisation. The most commonly involved antigen is D, followed by K, c and E. The maternal antibodies can cross the placenta and cause fetal haemolysis and anaemia, which, if untreated, may lead to fetal heart failure, hydrops and death. Fetal hydrops is the excessive accumulation of fluid in two or more fetal cavities that result in gross edema with occurrence of ascites, pleural and pericardial effusions. This serious clinical condition could lead to fetal death and significant perinatal mortality. Incidence of hydrops fetalis is about 1:3000 live born and among them 10–20% cases are immune hydrops [1]. Prophylactic use of anti-D has reduced the overall incidence

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of immune hydrops but inadvertent omission or inadequate dosing and other rare antigens are responsible for immune alloimmunisation. Historically, hydrops was felt to be a harbinger of fetal demise, but advancements in fetal treatment have improved outcomes for such condition. Nevertheless, mortality still approaches 40–50% when considering overall hydropic fetuses [2, 3] and predicting survival remains a challenge. Fetal therapy by intra-uterine transfusion (IUT) in immune hydrops is successful and in our clinical study markedly reduced the incidence of perinatal mortality. Our study also shows the various clinical characteristics of immune fetal hydrops and perinatal outcome in our patients over a vast period of 16 years.

Material and Methods

A retrospective study was performed in pregnant women with immune fetal hydrops from October 2004 to December 2019 in our tertiary care hospital where 3 Maternal–Fetal medicine specialists were available and all of them were trained from India and abroad. Local institutional ethical committee approved the study protocol. Fetal hydrops was defined as an abnormal fluid collection in two or more areas of the fetal body like peritoneal cavity, pleural cavity, pericardial cavity and skin. Placentomegaly and polyhydramnios were frequently associated with fetal hydrops, but they are not used as diagnostic criteria. We have differentiated immune hydrops with nonimmune hydrops by Rh negative blood groups, indirect coomb's test (ICT) with determination of different antigen status like D, K, c and E. All pregnant ladies underwent ultrasonography for detection of fetal hydrops and middle cerebral artery (MCA) Doppler for detection of fetal anaemia. Fetal anaemia was diagnosed whenever middle cerebral artery (MCA) peak systolic velocity (PSV) was > 1.5 MOM (Fig. 1) at a period of gestation as per Maire et al. chart [4, 5]. After evaluation intra-vascular IUT was performed in fetuses either by canulating umbilical vein (UV) or intra-hepatic vein (IHF). The choice between UV/ IHV was by the ease and expertise of the operator. Fresh blood with adequate level of 2,3 diphosphoglycerate, CMV-negative, leukocyte depleted, irradiated by 25 Gy to prevent GVHD (Graft versus Host Disease), Type-O, RhD-negative donor RBCs, cross-matched to a maternal sample and packed to a Hct (Hematocrit) of 75–80% to reduce volume overload, were used for IUT. Blood volume was calculated by using the Mandelbrot's formula for intravascular transfusion:

Intravascular volume = EFW X 0.14 X (Hct Target—Hct Initial)/ Hct transfused blood.

The final target hematocrit was 40% to 60%. Due to decreased cardiac reserve and increased susceptibility to volume overload hydropic fetus had poor outcome as compared to nonhydropic fetuses. Our aim was not to raise the Hb/Hct more than four-fold or in most cases to 50% above pretransfusion level, and it was followed by second transfusion after 3 to 7 days to reach target Hb/ Hct. The requirement of next IUT was decided by either following rate of drop of fetal haemoglobin at approximately 0.4 g/dL per day or drop of hematocrit at 1% per day or MCA PSV > 1.69 MoM for that gestational age (GA). For subsequent transfusion, the inter transfusion interval was individualized based on the underlying pathology, fetal condition and posttransfusion fetal hematocrit rather than MCA–PSV thresholds. All the patients received antenatal corticosteroids after 28 weeks of gestation. They were followed up and delivery was planned near 37 weeks of gestation. But many of them underwent emergency delivery

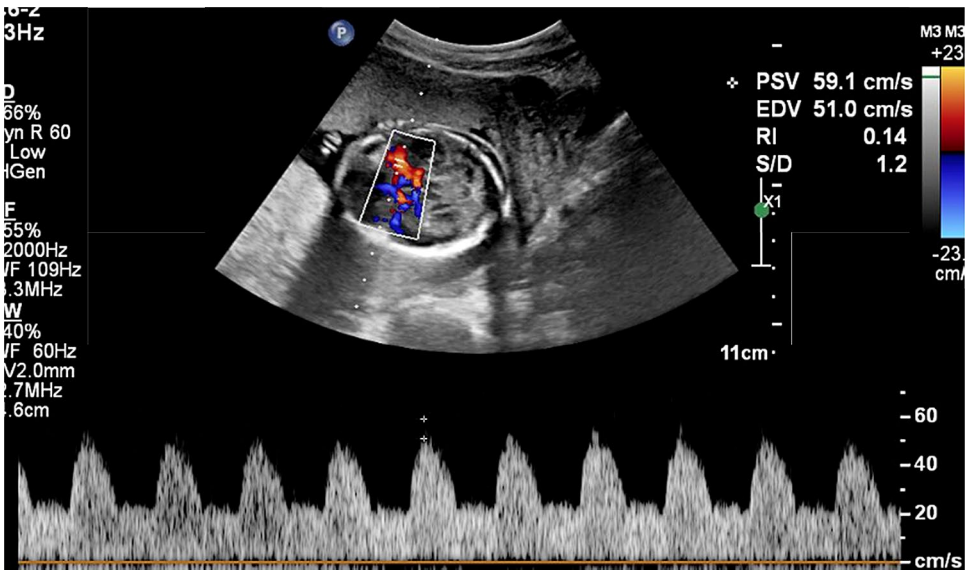

Fig. 1 MCA-PSV in a 19w fetus. Scalp edema of the fetus can be appreciated in the photograph

before 37 weeks for various obstetric reasons. After delivery all the fetuses were kept in NICU for observation. All the newborns underwent phototherapy and most of them received IVIg with a few receiving exchange transfusions. All the fetuses were followed up till 3 months postdelivery. Data were collected and analysed by using SPSS software and p value < 0.05 considered significant.

Table 1 Maternal characteristics of hydropic fetuses

Characteristics	< 32 weeks (n = 48)	≥ 32 weeks (n = 15)	*P* value
Age	26.2	25.8	> 0.05
BMI	22.8	23.1	> 0.05
Parity	2.3	2.9	> 0.05
Average gestational age of diagnosing hydrops	24.2	32.5	–
H/O anti-D: Received Not received	22 (45.8%) 26(54.2%)	8(53.3%) 7(46.7%)	> 0.05 > 0.05
ICT status	1:64–1:2048	1:32–1:1024	–
Co-morbidity: Hypertensive disorders of pregnancy Gestational diabetes Anaemia (Hb < 10 Gm%)	17(35.4%) 12(25%) 21(43.7%)	5(33.3%) 4(26.6%) 7(46.7%)	> 0.05 > 0.05 > 0.05

Result

For analysis of hydropic fetuses we have divided them in two groups: First group (Group A) included fetuses reported to fetal medicine centre below 32 weeks period of gestation (POG) and second group (Group B) included fetuses diagnosed to have hydrops after 32 weeks POG. Average maternal age was 26 years, and most of them had normal BMI. 46% mothers received anti-D prophylaxis following delivery or abortion in group A, and 53% mothers received anti-D prophylaxis in group B. Average gestational age of diagnosing hydrops was 24.2 weeks in group A as compared to 32.5 weeks group B. Hypertensive disorders of pregnancy, gestational diabetes and maternal anaemia were the common associated co-morbid conditions (Table 1). Among the fetal ultrasound features, all the fetuses had ascites (Fig. 2). Most of them had pleural effusion, skin edema (Fig. 3) and pericardial effusion. Polyhydramnios and placentomegaly (Fig. 4) was frequently associated with hydrops. Pericardial effusion was present in 81% fetuses in Group A as compared to 53% fetuses in Group B, and it was found to be statistically significant (Table 2).

The youngest hydropic fetus received IUT by intravascular route was at 18 week and 3 days POG. The same fetus received combined transfusion through intra-peritoneal and intra-vascular route at 20-week gestation. Most of the fetuses received IUT via umbilical vein and one fetus received IUT via intra-hepatic vein. Most of the fetuses received 3–4 IUT with maximum 7 times in four fetuses. Pretransfusion

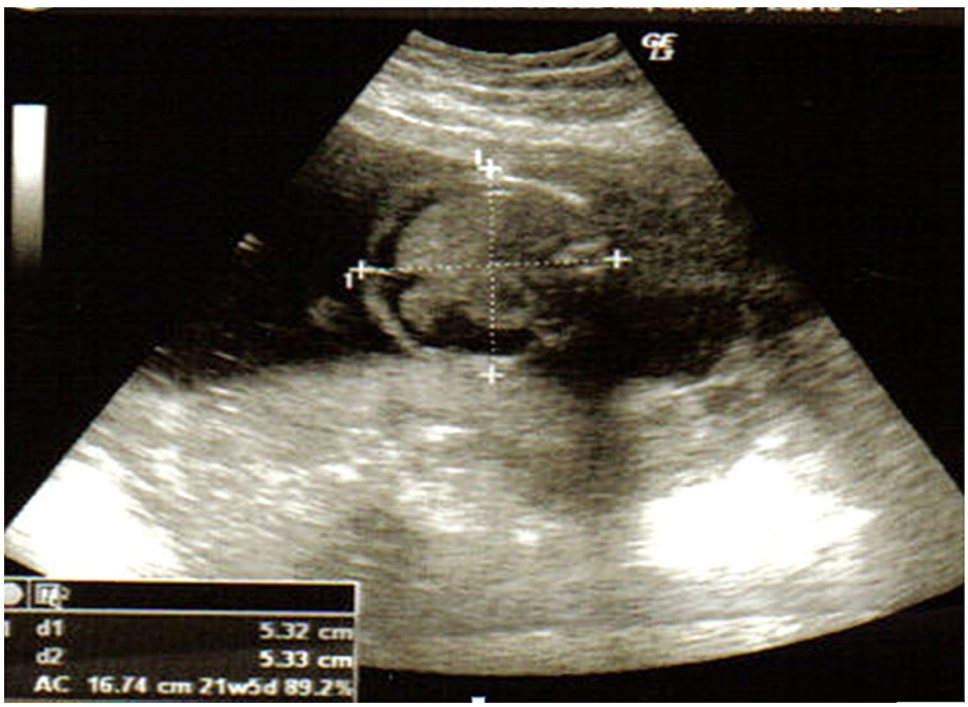

Fig. 2 Fetal ascites in a 18w fetus

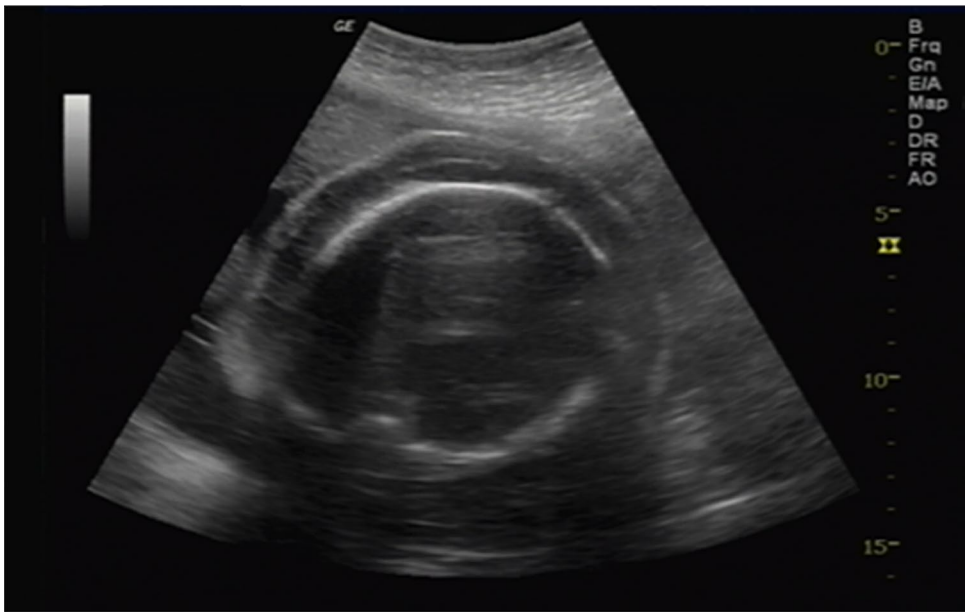

Fig. 3 Fetal scalp edema

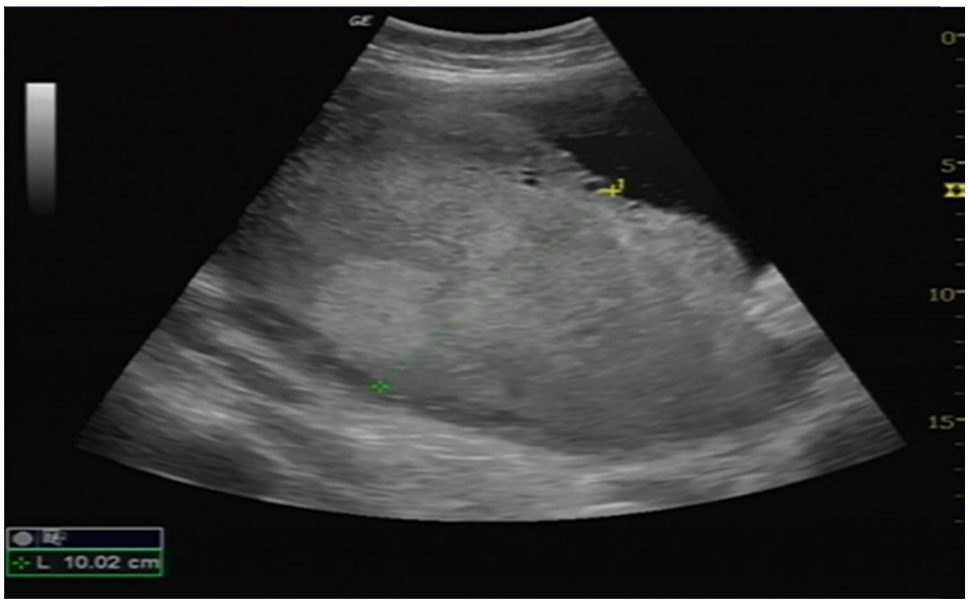

Fig. 4 Placentomegaly (10 cm placental width at 24 weeks of gestation)

Table 2 Fetal characteristics of hydropic fetuses

Hydropic Characteristics	< 32 weeks (n = 48)	≥ 32 weeks (n = 15)	*P* value
Ascites	48(100%)	15(100%)	> 0.05
Pleural effusion	47(98%)	15(100%)	> 0.05
Pericardial effusion	39(81%)	8(53.3%)	**< 0.05**
Skin edema	43(89.5%)	12(80%)	> 0.05
Cardiomegaly	46(95.8%)	14(93.3%)	> 0.05
Placentomegaly	47(98%)	13(86.6%)	> 0.05
Polyhydramnios	44(91.6%)	12(80%)	> 0.05
Fluid present in all four compartments	31(64.5%)	9(60%)	> 0.05

haemoglobin was below 5 gm% in almost all the cases. Complete resolution of hydrops was seen in 90% of hydropic fetuses and average time taken for resolution of hydrops was 11 days (Table 3). One of such neonate had gross ascites (Fig. 5) which was required to be drained for 10 days by a continuous peritoneal drain in neonatal intensive care (NICU). Gestational age at delivery was 34.2 weeks in group A, and it was 36.4 weeks in group B. Most of the fetuses after delivery received phototherapy and intravenous immunoglobulin (IVIg) and 10% fetuses received exchange transfusion in Group A (Table 4). During the treatment period, we lost 5 babies that included 03 intra-uterine deaths and 02 neonatal deaths. All the babies were doing well till

Table 3 Fetal therapy instituted in fetuses with hydrops

Therapy	< 32 weeks (n = 48)	≥ 32 weeks (n = 15)	*P* value
Intra-uterine transfusion: Intravenous transfusion	48(100%)	15(100%)	> 0.05
Umbilical Vein	47(98%)	15(100%)	> 0.05
Intrahepatic vein	01(2%)	-	-
Intra-peritoneal transfusion	01	-	-
Pretransfusion Hb (gm%)	4.3	4.6	> 0.05
Posttransfusion Hb (gm%)	12.2	13.1	> 0.05
Total no of IUT before delivery	3.6	2.9	> 0.05
Interval between 1st and 2nd IUT	2.1	2.4	> 0.05
Interval between 2nd and 3rd IUT	9.6	10.2	> 0.05
Complete resolution of hydrops	41 (85.4%)	14 (93.3%)	> 0.05
No of days taken for complete resolution of hydrops after 1st IUT	11.2	10.9	> 0.05

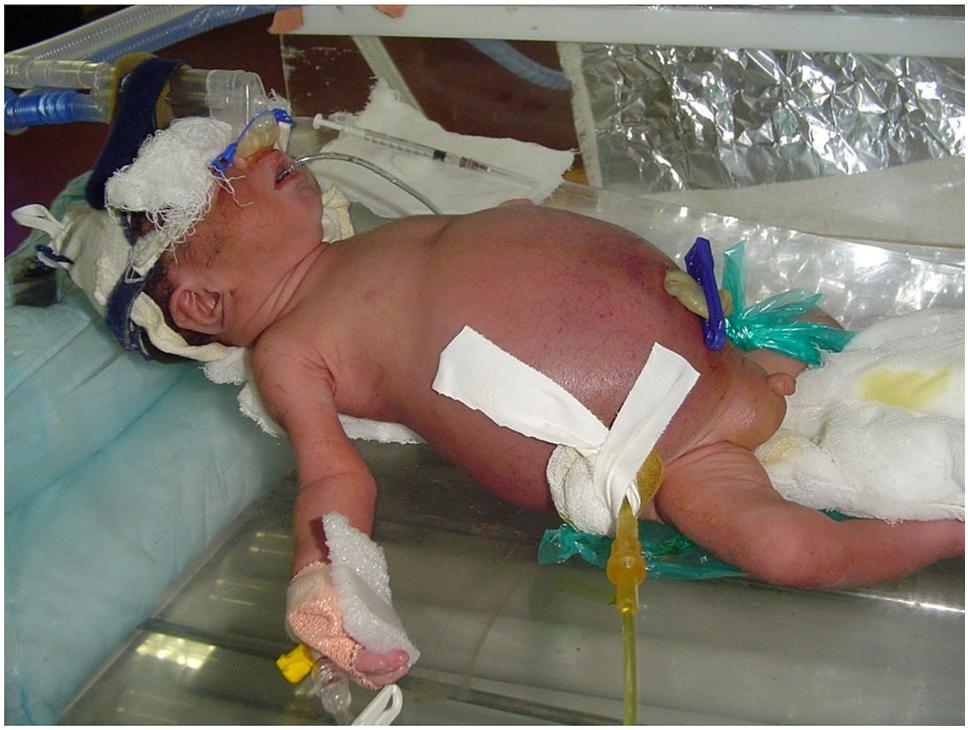

Fig. 5 Hydropic baby being nursed in neonatal intensive care unit. The two day old baby has gross ascites with secondary hydrocele clearly seen in this picture. The ascitic fluid is being drained by continuous peritoneal drain placed in situ

Table 4 Perinatal outcome of hydropic fetuses

Outcome	< 32 weeks (n = 48)	≥ 32 weeks (n = 15)	*P* value
Average gestational age at delivery	34.2	36.4	> 0.05
Postdelivery cord blood Hb (gm%)	12.3	13.9	> 0.05
Postdelivery cord blood bilirubin (mg%)	6.2	5.8	> 0.05
Phototherapy	45(93.7%)	15(100%)	> 0.05
IVIg	43(93.7%)	14(93.3%)	> 0.05
Exchange transfusion	05(10.4%)	–	–

3 months postdelivery. We had successful perinatal outcome in about 92% of hydropic fetuses. Four fetuses presented with hydrops very early in gestation (below 21 weeks POG), and two of the fetuses had fluid in all four compartments. Both the neonatal death occurred in fetuses where complete resolution of hydrops was not achieved. Two fetuses had preterm premature rupture of membranes and one fetus had cord haematoma, but all these three fetuses survived with good Neonatal Intensive Care (Table 5).

Discussion

Hydrops fetalis is an emergent medical condition that requires urgent ultrasound evaluation, referral to a higher medical centre where Fetal Therapy and NICU (Neonatal Intensive Care Unit) facilities are available. Untreated hydrops has higher incidence of intra-uterine fetal death (IUFD) and neonatal mortality rate as high as 50–95% [6]. Prematurity, low Apgar score, severe acidosis and presence of pericardial effusion are the causes of higher rates of neonatal mortality [7]. All the hydropic fetuses in our study group were due to Rh-alloimmunisation. 50% of our patients were alloimmunised despite receiving anti-D immunoglobulin following delivery or abortion. It may be due to inadequate use of rhesus immune prophylaxis after potential sensitizing events like threatened abortion and administration of inadequate dose. Five of our mothers had anti-kell antibodies and one mother had anti-c antibody.

The development of hydrops is due to hepatic hypertrophy with portal hypertension and hepatocellular damage rather than fetal heart failure. With severe RBC destruction, hepatic erythropoiesis and hepatic enlargement become extreme and it results in portal and umbilical venous hypertension. The placenta becomes enlarged, placental perfusion is reduced and ascites appears. Hypoalbuminemia develops and produces generalized anasarca. Pleural and pericardial effusions appear in fetuses with severe affection. It explains the variable degree of fetal anaemia noted with Rh hydrops fetalis because the degree of hepatic hypertrophy, portal hypertension and hepatocellular damage—not anaemia—are its basic causes. Although anaemia usually is severe, hydrops may occur with haemoglobin levels well above 7 g/dL, but usually it is below 5 g/dL [8, 9]. In our study all the hydropic fetuses had ascites and most of the cases had placentomegaly and polyhydramnios in ultrasound.

Fluid collection in 3 or more compartments has higher mortality [10] as compared to fluid collection in 2 compartments [11]. In our cohort, fetal survival did not depend on the number of compartments involved. Almost 60% fetuses had fluid in all four compartments. Involvement of 3 or 4 compartment hydrops is simply a late manifestation of all of the disease processes. We did not find presence of placentomegaly and polyhydramnios as an indicator of severity of disease and they are not related to perinatal survival. Previous studies reported that presence of pleural effusion was a poor prognostic factor of fetal hydrops [12]. In our study, pleural effusion was present in almost all cases and it was not found to be an indicator of fetal survival.

Intravenous IUT is always preferred over intra-peritoneal blood transfusion [8], and in our treatment protocol we have used 100% intravenous IUT. Only one fetus received combined transfusion at 20-week POG to delay the third transfusion for achieving fetal growth. Complete resolution of hydrops achieved in 87% of fetuses and one had intrauterine death at 29 weeks POG. IUT given at earlier gestation is an important cause for multiple transfusions. Fetal hydrops diagnosed after 32 weeks gestation, all the fetuses in our study had favourable outcome. We found that, earlier the gestation of development of hydrops and not achieving complete resolution of hydrops before delivery are important factors in outcome of hydropic fetuses.

We acknowledge the fact that our study is limited by a single-centre study. However, our findings are important as it includes 63 immune hydropic fetuses over a period of 16 years for understanding the characteristics of the disease, treatment and pregnancy outcome.

Conclusion

Favourable perinatal outcome can be achieved by intra-uterine blood transfusions in cases of fetal hydrops due to Rh alloimmunisation. Fetal hydrops diagnosed later in gestation

Table 5 Complications during treatment of hydropic fetuses

Complications	< 32 weeks (n = 48)	≥ 32 weeks (n = 15)	*P* value
Cord hematoma	01 (2%)	–	–
Preterm premature rupture of membrane	02 (4.1%)	–	–
Emergency caesarean required immediately after IUT	–	–	–
Fetal death	03 (6.2%)	–	–
Neonatal death	02 (4.1%)	–	–

and complete resolution of hydrops before delivery are good prognostic factors.

Compliance with ethical standards

Conflict of interest Devendra Arora, Reema Kumar, Sanjay Singh and Madhusudan Dey declare that they have no conflict of interest.

Informed Consent Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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