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ORIGINAL ARTICLE

Nonimmune Hydrops Fetalis: Factors Which Predict Outcome

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Abstract

Aims and Objective To evaluate the cause of NIHF cases referred to a tertiary referral center and to analyze the outcome.

Materials and Methods A total of 130 cases of fetal hydrops registered during eight-year study period were reviewed. Antenatal ultrasound, blood investigations and postnatal fetal examination were done, and outcome was noted.

Results Out of 130 cases of NIHF, antenatal ultrasound showed the presence of structural malformations in 94/130 (72.3%), cardiac abnormality was the most common (34/130, 26.1%) and cystic hygroma was seen in 15/130 (11.5%). Chromosomal abnormality was observed in 15(11.5%) cases, and Doppler US showed anemia in 4/130 (3.1%) cases only. Live born were 25 (12.9%), and rest all were stillborn or abortion. Later mean gestational age of presentation ($p = 0.0001$), presence of gastrointestinal malformation ($p = 0.0001$) and absence of structural malformations ($p = 0.0441$) were factors significantly associated with live birth; the presence of cystic hygroma ($p = 0.0431$) or structural heart defect ($p = 0.007$) was significantly associated with poor outcome.

Conclusion Fetal anemia was not a common cause of NIHF in the study population. The early onset of hydrops and

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presence of structural malformation carry a graver prognosis; type of structural defect also has bearing on outcome.

Keywords Nonimmune hydrops · Prenatal diagnosis · Ultrasound

Introduction

Hydrops fetalis is defined as the abnormal accumulation of fluid in at least two different fetal compartments [1]. It usually presents as subcutaneous edema, accompanied by effusions in two or more serous cavities including pericardial or pleural effusions and ascites. Polyhydramnios and increased placental thickness is generally an associated finding [2]. With improved treatment and diagnosis of rhesus iso-immunization, nonimmune factors have become a more frequent cause of hydrops fetalis. The incidence of nonimmune hydrops fetalis (NIHF) is estimated at 1 in 3000 pregnancies [3]. The pathophysiology of NIHF is complex, and the causes are numerous. There is no consensus on etiological categories used to classify NIHF; studies have found that the causes for overlap [3], for example a case with trisomy 21 with a major cardiac anomaly, can be grouped as cardiac as well as chromosomal causes. Antenatal ultrasonography (US) plays an important role in diagnosis of NIHF; a classification based on different structural anomalies associated with NIHF is likely to be more appropriate.

Previous studies have shown favorable outcome in 20–27.5% cases of NIHF [3, 4], although some studies have been carried out to determine the prognostic factors leading to a good outcome, but more studies are needed. Also the cause and outcome of NIHF in Indian population have not been studied before.

The aim of the study was to evaluate the cause and outcome of NIHF in our setting. We intended to classify causes, according to structural abnormality detected on US. We also intended to find whether there was an association of antenatal factors such as gestational age at presentation, polyhydramnios or type of structural anomaly with respect to outcome.

Materials and methods

During the study period of eight years (July 2008–June 2016), all women with NIHF diagnosed on ultrasound were investigated and prospectively followed till delivery. Institute's ethical clearance was taken before the study. Informed consent was obtained before including the subjects in the study.

Demographic characters such as age, consanguinity, gravida, parity, abortion and mean age of presentation were noted. Detailed maternal history was obtained with emphasis on consanguinity, diabetes, history of fever with rash. Maternal blood tests were done for blood cell count, blood grouping and presence of rhesus factor, hemoglobin electrophoresis, indirect Coomb's test, antibody screening for infections such as toxoplasmosis, rubella and cytomegalovirus and VDRL test for syphilis. A detailed US was done with targeted imaging of each system. Amount of liquor and placental thickness were observed. Fetal echocardiography was done. Middle cerebral artery peak systolic velocity for fetal anemia was measured and compared to the existing chart for fetal anemia [6]. Counseling for invasive testing was done and was performed when consents were given; sample was sent for karyotyping and genetic testing. Review ultrasound was done at regular intervals to see the evolution of the anomaly and for development of new findings. The women were followed till delivery. The stillborn babies were examined externally, internal examination was done after consents, and relevant tissue was sent for histopathological examination. Counseling was provided after collecting all reports, and the chance of recurrence was explained.

Results

During the study period of eight years, there were 147 cases of hydrops fetalis, 10 were lost to follow-up. Of 137 cases, 7 (10.4%) had immune hydrops and 130 cases had nonimmune hydrops. Table 1 shows the epidemiological profile of women with antenatal diagnosis of NIHF. Nearly half of the women (61/130, 46.9%) were nulliparous. There was a previous history of abortion in 22/130 (16.9%). Consanguinity was present in 5.4%. The women most commonly presented between 28 and 34 weeks of gestation (53/130, 40.8%); only 25/130 (20%) women presented before 20 weeks gestation.

The structural malformations observed in NIHF cases are given in Table 2. The targeted ultrasound revealed structural defect in 94/130 cases (72.3%), and there was no significant finding on US in the rest 36(27.3%) cases. Abnormality in cardiovascular system was most commonly seen (34/130, 26.1%), structural cardiac defect was seen in 21/130 (16.1%) cases, and most of the defects were multiple and involved the right side of heart. Two cases of supraventricular tachycardia were successfully managed with transplacental tablet sotalol. Cystic hygroma with hydrops was seen in 15/130 (11.5%) cases (Fig. 1), all of them presented early in gestation, and karyotyping showed Turner syndrome as the most common anomaly (9/15).

Table 1 Epidemiological profile of women with antenatal diagnosis of NIHF in fetuses

Antenatal characteristics	Total number ($n = 130$)	Percentage of total (%)
Age (years)		
18–22	29	22.3
23–26	56	43.0
27–30	25	19.2
31–34	15	11.5
>34	5	3.8
Parity		
0	61	46.9
1	42	32.4
2	19	14.5
3	8	6.2
Consanguinity		
Present	7	5.4
Abortions		
1	17	13.1
2	5	3.8
Type of pregnancy		
Singletons	125	96.2
Twins	5	3.8
Gestational age at presentation		
≤20 weeks	26	20.0
21–27	37	28.5
28–34	53	40.8
>34	14	10.7

There were 3 cases with congenital cystic adenomatoid malformation (CCAM) and hydrops, and all of them were microcystic and received two doses of injection betamethasone 12 mg, 24 h apart; in one case, there was decrease in size with subsequent survival. The gastrointestinal malformations ranged from echogenic bowel to calcifications and pseudocyst formation, suggestive of meconium peritonitis. The outcome was significantly better in cases with gastrointestinal malformation ($p = 0.0001$) (Table 3).

The middle cerebral artery, peak systolic velocity (PSV) showed severe anemia in 4 cases. Alpha thalassemia was diagnosed in two of them; in one case, the hydrops improved on follow-up US, and baby was live born; one other case was stillborn. Blood sugar was deranged in 7 cases. Acute phase titers for TORCH infection showed positive titers in 8 cases (3 each for toxoplasma and CMV and 2 were rubella positive). Chromosomal abnormality was found in 15 cases. The most common abnormality was 45 XO.

Stillbirth or abortion occurred in 105/130 (88.7%) cases, the baby was examined after birth in all cases, and internal examination was done after consents in 45/105 (42.9%); in 25 cases, additional findings were present on examination. Additional findings included the presence of contractures, pterygium, cataract and cleft palate in 2 cases (Fig. 2), and were diagnosed as Pena–Shokeir syndrome. Asphyxiating thoracic dysplasia (2 cases) and osteogenesis imperfecta (one case) were diagnosed after infantogram (Fig. 3). There was extramedullary hematopoiesis on histopathology of liver and spleen in three cases with fetal anemia. Placental histopathology showed presence of inflammatory

Table 2 Systemwise structural malformations in NIHF cases

Causes	No of cases	%
CNS	**10**	7.7
Anencephaly	1	0.8
Hydrocephalus	3	2.3
Microcephaly	2	1.5
Dandy walker malformation	3	2.3
Agenesis of corpus callosum	1	0.8
CVS	**34**	26.1
Structural heart defect	21	16.1
Rhythm disturbance	6	4.6
Cardiomegaly	7	5.4
Neck and thorax	**19**	14.6
Cystic hygroma	15	11.5
Thoracic duplication cyst	1	0.8
CCAM	3	2.3
GIT	**7**	5.4
Echogenic bowel	5	3.8
Intraabdominal varix	1	0.8
Omphalocele	1	0.8
Musculoskeletal skeletal	**11**	8.5
Osteogenesis Imperfecta	1	0.8
Asphixiating thoracic dysplasia	2	1.5
Short long bones	2	1.5
Fetal akinesia syndrome	6	4.6
Renal	**5**	3.8
Hydronephrosis	2	1.5
LUTO	2	1.5
MCK	1	0.8
Twin complications	**4**	3.1
TTTS	3	2.3
TRAP	1	0.8
No abnormality on US	**36**	27.7
Anemia—MCA PSV	**4**	3.1
Total	**130**	100

P value of less than 0.05 is taken as significant and is marked in bold

CNS central nervous system, *CVS* cardiovascular system, *CCAM* congenital cystic adenomatoid malformation of lung, *TTTS* twin–twin transfusion syndrome, *TRAP* twin reversed arterial perfusion, *URSM* urorectal septal malformation, *MCA PSV* middle cerebral artery peak systolic velocity

Table 3 Analysis of factors affecting outcome of nonimmune hydrops cases

Antenatal/postdelivery finding	Live (25)	Stillborn (105)	*p* value
Age	26 years (20–36)	25 (19–35)	0.706
Parity	0.8 (0–3)	0.7 (0–4)	0.297
Consanguinity	1	6	0.257
Gestation at detection	30.6 (22–38)	25.1 (13–36)	**0.0001**
Polyhydramnios	4	33	0.087
Increased placental thickness	0	5	0.432
CNS malformation	0	10	0.088
Cystic hygroma	0	15	**0.0431**
Heart arrhythmia	2	4	0.383
Structural heart defect	0	28	**0.007**
Thoracic malformation	1	3	1.000
Gastrointestinal abnormality	5	2	**0.0001**
Urogenital system	2	3	0.260
Musculoskeletal	0	11	0.0994
Twin complications	1	3	1.000
No abnormality on US	11	27	**0.0441**
Middle cerebral artery PSV showing anemia	1	3	1.000

P value of less than 0.05 is taken as significant and is marked in bold

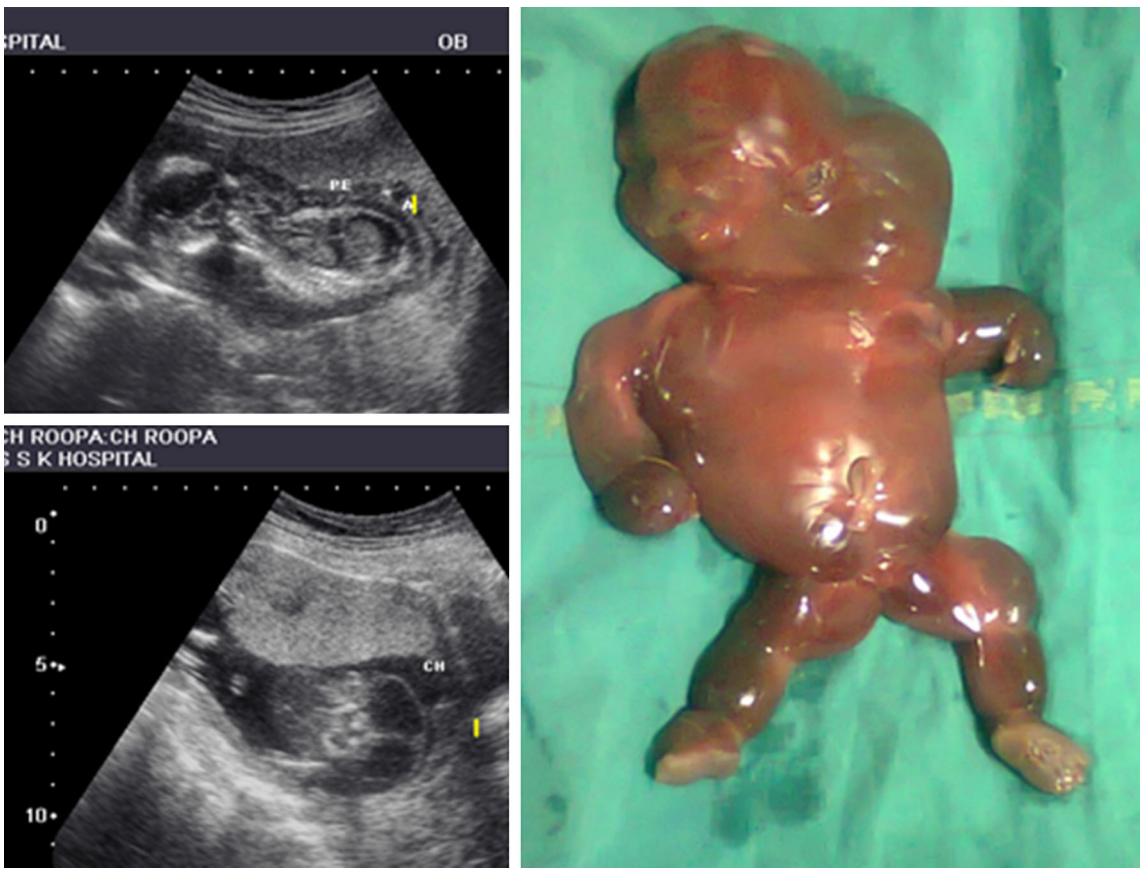

Fig. 1 The ultrasound and photograph of the baby with cystic hygroma and hydrops. The karyotype of the baby was 45 XO

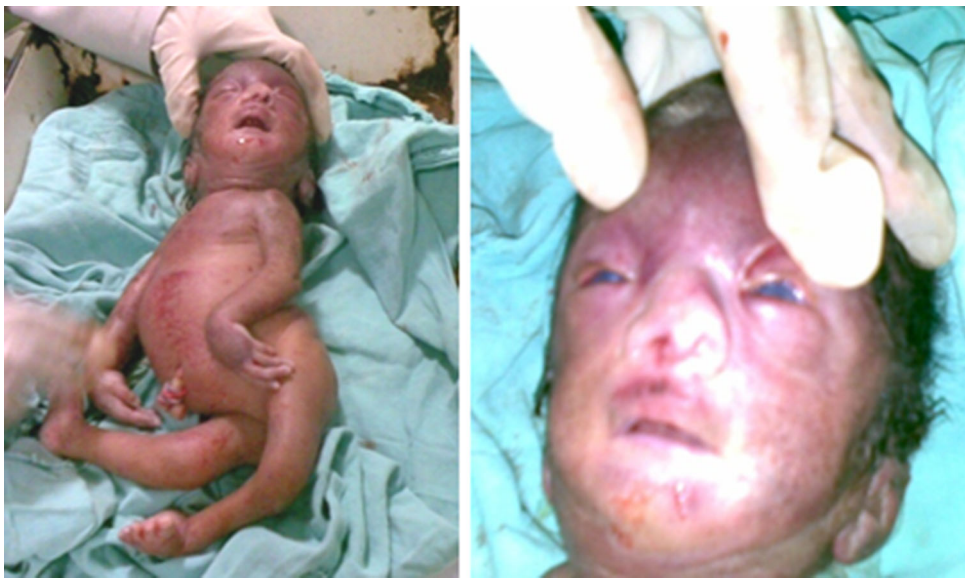

Fig. 2 Stillborn baby with contracture deformity, cleft palate and cataract along with h drops. The findings were suggestive of Pena–Shokier phenotype

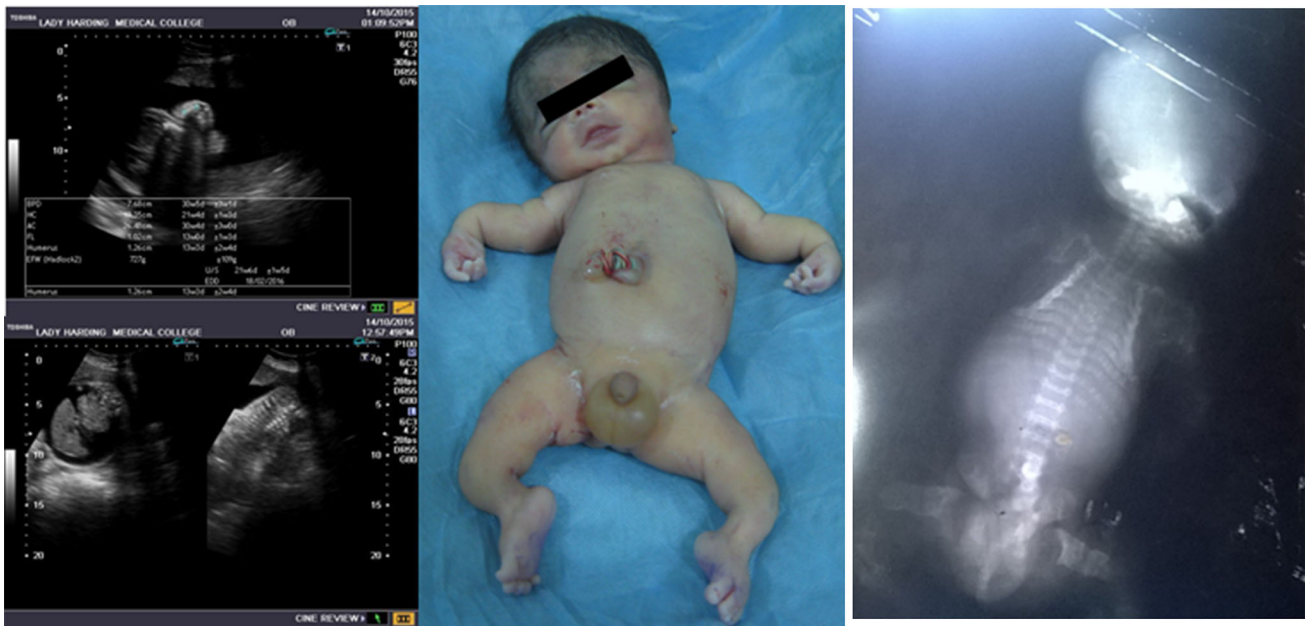

Fig. 3 The ultrasound, postnatal photograph and infantogram of the baby with hydrops. Short limbs, fracture and bending of long bones seen, the findings were consistent with Osteogenesis Imperfecta type II

markers in 5 cases with positive serology for infections. One baby had hairy body, synophrys, heart defect, short stature features suggestive of Cornelia De Lange syndrome. There was a case with absent radius and thumb, atrial septal effect findings suggestive of Holt–Oram syndrome, and one baby with complex heart defect had right isomerism, suspected on internal examination as spleen was absent with centrally located liver. There were hypertelorism, micrognathia, broad root of nose, pulmonary stenosis and atrial septal defect; these features were suggestive of Noonan syndrome. There was prune belly syndrome in two cases. There were three cases with fetal akinesia syndrome or joint contractures; there was first-degree consanguinity in two of them, and prenatal testing for storage disorder was done in one case only which was negative. There was one case with thoracic duplication cyst (Fig. 4).

The analysis of antenatal factors leading to poor outcome showed that early gestational age at detection ($p = 0.0001$) was associated significantly with poor outcome. Among fetal structural anomalies, cystic hygroma ($p = 0.0431$) and cardiac defect ($p = 0.007$) were

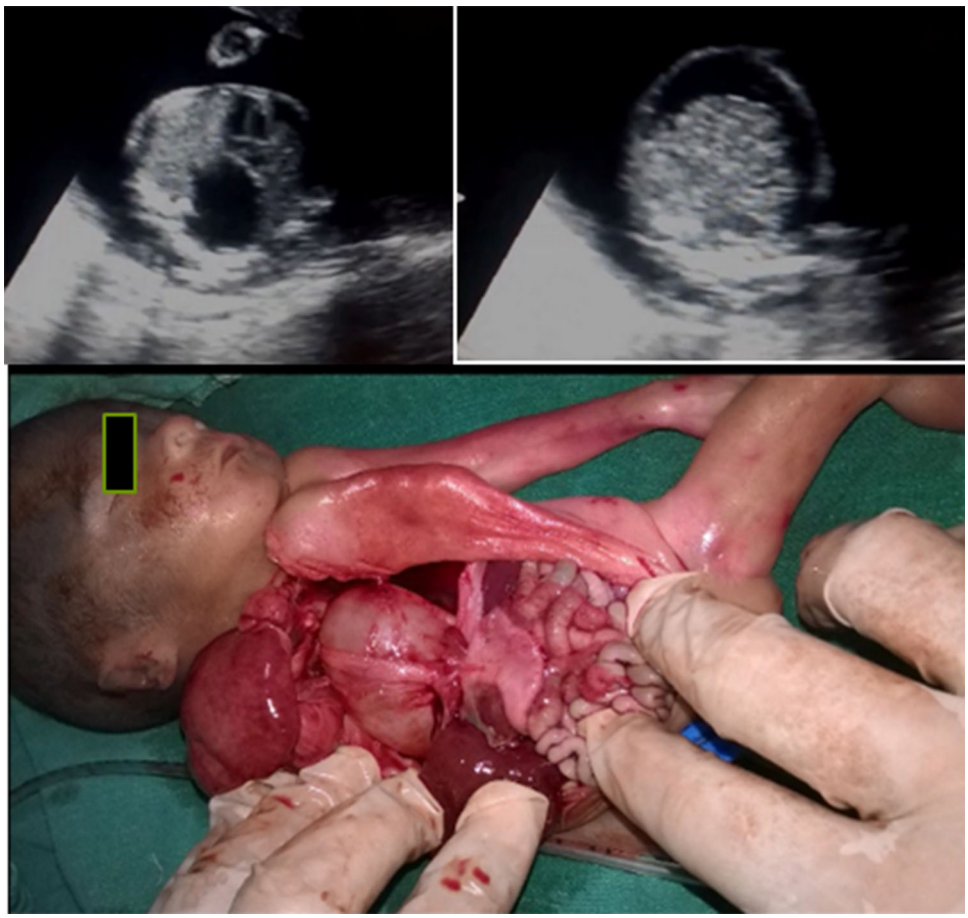

Fig. 4 The ultrasound picture shows a cystic structure in the thoracic cavity posterior to the heart. The autopsy picture shows the location of cyst posterior to the esophagus, findings suggestive of duplication cyst

associated with poor outcome, whereas gastrointestinal abnormality ($p = 0.0001$) was associated with significantly better outcome. The cases in which no abnormality was found on US had significantly better outcome ($p = 0.0441$) than those in which there was presence of structural anomaly.

Discussion

Hydrops is not a disease, but the endpoint of diverse causes. The highlight of the study was to determine and classify structural defects associated with NIHF in a large cohort of 130 cases and to determine factors which determine the outcome of such cases.

Bellini et al. [3] recently published an update on their earlier review of causes of NIHF, and they pointed out that it was frequently difficult or impossible to correctly classify patients with a chromosome imbalance, since they could be classified either in the chromosomal category or in the (presumed) pathogenetic mechanism leading to the hydrops, such as the cardiovascular abnormality. Therefore, in the present study NIHF cases were classified as structural anomaly associated with hydrops, which lead to better categorization and no overlap among each other. Other causes such as chromosomal anomaly, infections, inherited inborn errors of metabolism and syndromes were described separately.

In the present study, the cardiac defect was the most common abnormality (26.1%), consistent with study by Bellini et al. [3], who reviewed published reports between 2007 and 2013 and found the incidence of cardiovascular abnormality to be 20.1%. Chromosomal abnormality was seen in 11.5% cases in the present study; Bellini et al. [3] reported it to be present in 9% in their review. Anemia was not a major cause in our population as was present in only 3.2% cases on Doppler US, whereas it was present in 9.3% cases (4.2–14.4) in the study by Bellini et al. [3]. The lower incidence may be due to the prevalence of the milder form (alpha/alpha alpha) of alpha thalassemia in the local population [5]; thus, the incidence of alpha thalassemia leading to hydrops was far lower in the study population.

The outcome of NIHF in terms of live birth was 25%, which was similar to previous studies [5, 6]. The analysis of the antenatal factors which influenced outcome revealed that the early mean gestational age of presentation ($p = 0.0001$) and the presence of any structural anomaly were associated with worse outcome. This might be

because the risk of fetal aneuploidy is higher when identified earlier in gestation or when fetal structural anomalies are seen; therefore, fetal chromosome analysis is indicated in all cases of hydrops [7]. Increased placental thickness has been found to be associated with alpha thalassemia and therefore associated with poor prognosis if found in cases with NIHF [7].

Among the anomalies, the presence of gastrointestinal malformation ($p = 0.0001$) was more significantly associated with live birth, whereas the presence of cystic hygroma ($p = 0.0431$) or structural heart defect ($p = 0.007$) was associated with significantly poor outcome. Poorer outcome of cystic hygroma might be due to the high association of the chromosomal anomaly with cystic hygroma [8]. Association of heart defect with hydrops generally signifies a failing heart, and the structural lesions that result in right atrial pressure or volume overload are more commonly associated with hydrops fetalis [9]. Intraabdominal masses may cause NIHF due to obstruction of venous return, while gastrointestinal obstruction and infarction may lead to decreased colloid osmotic pressure due to protein loss [10]. In the study by Yeom et al., the clinical characteristics affecting outcome were looked at; they found that fetal death and neonatal mortality rate were not significantly associated with Doppler velocimetry indices or location of fluid collection, but increasing numbers of the fluid collection sites were significantly associated with a higher risk of neonatal death [6]. In the study by Kim et al., prognostic scoring was done by the number of fluid compartments present; they demonstrated positive correlation between number of compartments involved and outcome [11].

The limitation of the study was that investigations such as prenatal tests for inborn errors of metabolism were not done in all cases and syndromes were suspected on phenotypic presentation only. The strengths were a large cohort and collection of data from Indian population and determination of factors which have significant bearing on outcome of hydrops cases.

Compliance with Ethical Standards

Conflicts of interest No conflict of interest among authors.

Human and Animals Rights Due consents were taken from human participants, and there were no animal participants in the study.

Informed Consent Informed consent was taken on predetermined proforma.

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