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ORIGINAL ARTICLE

Perinatal outcomes of 91 cases of non-immune hydrops fetalis

[1]Emre ERDOĞDU
[2]Resul ARISOY
[3]Lütfiye UYGUR
[4]Selim SANCAK
[1]Furkan KAYABAŞOĞLU
[5]Sevcan Arzu ARINKAN
[3]Oya PEKİN
[6]Murat MUHCU

[1]Department of Perinatology, Alle Health Clinic, İstanbul, Türkiye

[2]Department of Perinatology, Ataşehir Memorial Hospital, İstanbul, Türkiye

[3]Division of Perinatology, Department of Obstetrics and Gynecology, University of Health Sciences, Türkiye. Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Türkiye

[4]Division of Neonatology, Department of Pediatrics, University of Health Sciences, Türkiye. Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Türkiye

[5]Department of Obstetrics and Gynecology, Haydarpaşa Training and Research Hospital, İstanbul, Türkiye

[6]Department of Perinatology, Ümraniye Training and Research Hospital, İstanbul, Türkiye

ORCID ID
EE : 0000-0003-3305-9925
RA : 0000-0003-1359-1674
LU : 0000-0002-6325-1910
SS : 0000-0003-3952-9203
FK : 0000-0003-4674-8850
SAA : 0000-0002-0034-372X
OG : 0000-0001-6347-5845
MM : 0000-0001-7039-375X

ABSTRACT

Objective: We aimed to investigate the proportion of etiologically identified non-immune hydrops fetalis (NIHF) cases and perinatal outcomes of all the cases that were diagnosed and managed in a single tertiary perinatal center over a 7-year period.

Material and Methods: Perinatal outcomes, background disorders, and clinical details of the patient and the surviving fetus were retrospectively analyzed.

Results: The etiology was identified prenatally in 60 (65.9%) out of 91 cases. Cystic hygromas and cardiac abnormalities were the most common identifiable causes. Of 91 cases, 48 (52.7%) elected to terminate their pregnancy. Among the 43 patients who elected to continue with their pregnancy, 12 (27.9%) resulted in intrauterine fetal death and 31 (72.1%) survived to birth. The survival rate at discharge was 23.2%.

Conclusion: NIHF is a complex problem associated with high mortality. Many patients elect the termination of their pregnancy, and the survival rate is 23.2% in cases who elect to continue with their pregnancy.

Keywords: Non-immune hydrops fetalis, perinatal outcome, survival.

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Correspondence: Lütfiye UYGUR, MD. Türkiye Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Perinatoloji Bölümü, İstanbul, Türkiye.
Tel: +90 216 391 06 80 **e-mail:** lutfiyeuygur@gmail.com

INTRODUCTION

Hydrops fetalis (HF) is a condition defined as the excessive collection of fluid in more than two body cavities and tissues in the fetus, and it occurs secondary to any pathophysiological process. HF can mainly be observed as immune and non-immune but with the decline of rhesus isoimmunization, almost 76–87% of all cases have a non-immune etiology.[1] Non-immune HF (NIHF) occurs at various gestational ages and has many etiologies, and the condition is associated with high mortality rates despite the improvements in diagnosis and management of the disease.[2]

This study aims to investigate the proportion of etiologically identified NIHF cases and perinatal outcomes of all antenatally diagnosed NIHF cases that were detected and managed in a single tertiary perinatal center over a 7-year period.

MATERIAL AND METHODS

We conducted a retrospective case series of prenatally diagnosed NIHF cases in the second and/or third trimester between 2008 and 2015 after having searched the archives of ultrasound database at our center. The study was approved by the local ethics committee.

All patients appropriately had detailed ultrasonographic scans and Doppler flow studies. NIHF was defined as fluid accumulation in two or more fetal body compartments (e.g., skin/scalp edema, ascites, pleural effusion, or pericardial effusion). Polyhydramnios was defined as an amniotic fluid index ≥24 cm or a maximum vertical pocket ≥8 cm. The cases of immune hydrops fetalis were excluded from the study after the clinical and laboratory examinations (according to the findings of maternal blood group and indirect Coombs test). Anemia was suspected on an elevated peak systolic velocity seen in the middle cerebral artery (>1.5 multiples of median) and was confirmed through fetal blood sampling. Fetal blood samples were tested for Parvovirus B19 infection through DNA detection using the nested polymerase chain reaction. A pediatric cardiologist was consulted to detect suspected cardiac problems through fetal echocardiograms. Fetal karyotype analysis and toxoplasma, rubella, cytomegalovirus, and herpes screenings were offered. After a thorough evaluation, the patient and her family were appropriately informed about the pregnancy outcome. Fetal interventions such as thoracoamniotic shunting, drainage of pericardial, pleural effusion, ascites, amniotic fluid reductions, in utero blood transfusions, and cardioversion of fetal arrhythmias were recommended for appropriate cases. Maternal characteristics, serological results, sonographic findings, pregnancy outcomes, postmortem examinations of those elected terminations, stillbirths, and neonatal deaths were recorded. Multiple pregnancies, cases with incomplete data, and no follow-up were excluded from the study.

All ultrasonographic examinations were performed by Voluson 730 Expert and Pro (GE Healthcare, Milwaukee, WI). Gestational ages were determined by the last menstrual period (LMP) in patients with a regular menstrual period that occurs every 21–35 days and were confirmed with first-or second-trimester ultrasound examination. In patients who did not know their LMP, the gestational ages were determined using the measurements of crown-rump length in the first trimester and biparietal diameter in the second trimester.

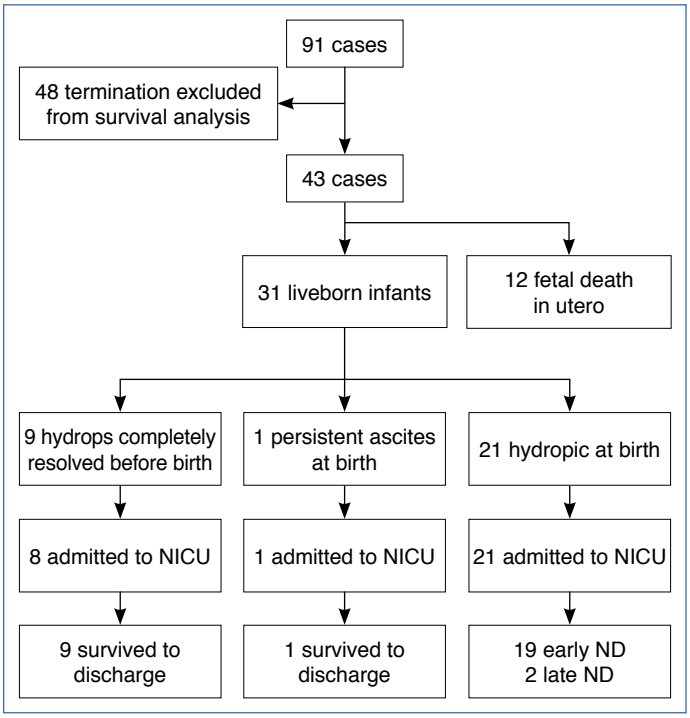

Figure 1: Flow chart of the cases.

Demographic data, fetal Doppler parameters, obstetric and perinatal outcomes were obtained from the medical database and the files of the patients. Patients with incomplete data were contacted by telephone to obtain the missing information.

The cases in this study were categorized into 12 groups according to the possible underlying etiology: Cardiac, thoracic, pulmonary, gastrointestinal, genitourinary, infectious, skeletal, chromosomal abnormality, genetic syndrome, anemia, non-chromosomal cystic hygroma, and unidentified causes. The chromosomal group consisted of cases with chromosomal abnormalities with associated structural defects. The cystic hygroma group included cases with congenital lymphatic disorders (mostly neck masses) who had normal karyotyping results. The remaining cases with no identified underlying etiology were classified as unidentified or idiopathic.

Statistical analysis was performed using SPSS v.11.5 (SPSS Inc., Chicago, IL. USA). Descriptive statistical methods (mean, standard deviation) were used to evaluate the obtained data. Comparison of variables was analyzed using the Chi-square test. A p value of 0.05 was considered statistically significant.

RESULTS

A total of 91 pregnancies complicated by NIHF were evaluated in the study. A flowchart of the cases is shown in Figure 1. The median maternal age was 27 years (range: 20–40 years), and the mean gestational age at diagnosis of fetal hydrops was 22 weeks (range: 15–36 weeks). Patient demographics are listed in Table 1. The most common presenting signs were ascites (92%), pleural effusion (80%), skin edema (84%), pericardial effusion (60%), and generalized edema (51%). Polyhydramnios was present in 14% of the patients.

Table 1: Characteristics of 91 cases with NIHF

	n (%) or Median (range)
Maternal age (years)	27 (20–40)
Fetal gender, female (%)	57
Gestational age at diagnosis (weeks)	22 (15–36)
Gestational age at delivery (weeks)†	31 (25.4–40)
Birthweight (g)†	2300 (770–4050)
Survival at discharge (%)†	23.2

†: Data after exclusion of terminated cases.

Fetal karyotyping was performed in 42 (46.1%) cases during the antenatal or postnatal periods. Chromosomal abnormalities were detected in 9 (9.8%) cases. The most common karyotype abnormality was monosomy X which was detected in 4 cases. There were also 3 cases of Trisomy 21, one case of Trisomy 13, and one case of 46, XX, inv(7)(p14p21). Table 2 summarizes the etiologies and pregnancy outcomes of these 91 fetuses with NIHF. The causes of NIHF were identified prenatally in 60 (65.9%) cases but could not be detected in the remaining 31 (34%) cases. Non-chromosomal cystic hygroma (17.5%) and cardiac abnormalities (17.5%) were the most common identifiable underlying causes of NIHF. These were followed by chromosomal abnormalities (9.8%), skeletal abnormalities (5.5%), infections (3.3%), gastrointestinal system abnormalities (3.3%), fetal anemia (2.2%), thoracic abnormalities (2.2%), genetic syndromes (2.2%), genitourinary abnormalities (1.1%), and fetal tumors (1.1%). Postmortem autopsies were performed in 18 cases, and the most common autopsy findings were found to be head and neck and urogenital tract abnormalities. Additional findings were revealed in five cases in postmortem examination. These findings included cleft palate, low set ear, cataract, pterygium, and contractures that suggested the diagnosis of Pena-Shokeir syndrome in one fetus. There were also hypertelorism, broad root of nose, pulmonary stenosis in one fetus that suggested Noonan syndrome. The family did not authorize genetic testing. There was another dysmorphic fetus with neck lymphangioma, cleft palate, depressed nasal bridge, and hypertelorism that suggested a syndromic condition. However, this case could not be clearly diagnosed. Crossed fused renal ectopia and horseshoe kidney were detected in two fetuses whose conditions were not thought to be associated with hydrops.

The distribution of all cases by etiology and gestational age at diagnosis is shown in Table 3. The most common diagnoses made before 24 weeks and between 24 and 28 weeks of gestation were idiopathic. Cystic hygroma and cardiac etiology were the most common identifiable causes diagnosed before and after 24 weeks of gestation, respectively. Cardiac etiology was the most common cause of NIHF, and it was diagnosed after 28 weeks of gestation.

Pregnancy outcomes are also summarized in Table 2. After intensive counseling, 48 of 91 cases (52.7%) elected to terminate their pregnancy. The remaining 43 cases (47.2%) elected to continue with their pregnancy. None of the cases with thoracic, genitourinary, skeletal abnormalities, genetic syndromes, and fetal tumors elected to continue their pregnancy. The cardiac abnormality group and the unidentified group had the lowest termination rates of 18.7% and 29%, respectively. Etiology was determined in 21 (49%) of 43 cases who selected to continue with their pregnancy. Of these 43 cases, cardiac abnormalities were the most common identifiable underlying cause in 11 (17.5%) cases. Of 43 cases, 12

Table 2: NIHF outcome and background disorder

Etiology	n	Non terminated cases	TOP	IUFD	Median GA at delivery†	END	LND	Survival to discharge
Cardiac	16	13	3	5	33.2 (28.3–40)	6	0	2
Cystic hygroma	16	2	14	0	26‡, 31.2‡	1	0	1
Thoracic	2	0	2	0	–	0	0	0
Gastrointestinal	3	1	2	0	35‡	0	0	1
Genitourinary	1	0	1	0	–	0	0	0
Genetic syndrome	2	0	2	0	–	0	0	0
Skeletal	5	0	5	0	–	0	0	0
Fetal tumor	1	0	1	0	–	0	0	0
Fetal anemia	2	2	0	1	35‡	0	0	1
Infections	3	2	1	1	38‡	0	0	1
Chromosomal	9	1	8	0	37‡	0	0	1
Unidentified	31	22	9	5	31.3 (25.4–38)	12	2	3
Total	91	43	48	12	31 (25.4–40)	19	2	10

TOP: Termination of pregnancy; IUFD: Intrauterine fetal death; END: Early neonatal death; LND: Late neonatal death; ‡: Gestational age (GA) at delivery is mentioned for each patient due to the small number of patients; †: Cases after termination of pregnancy.

Table 3: Etiology and gestational age at diagnosis of all cases

Etiology	Total	<24 gestational week	24–28 gestational week	>28 gestational week	Median gestational age at diagnosis
Cystic hygroma	16	16	0	0	19 (19–22)
Cardiac	16	11	1	4	20 (19–34)
Thoracic	2	1	1	0	23 (21–26)
Gastrointestinal	3	2	0	1	25 (21–34)
Genitourinary	1	1	0	0	23
Skeletal	5	5	0	0	17 (15–22)
Genetic syndrome	2	2	0	0	17 (15–30)
Fetal tumor	1	0	1	0	24
Fetal anemia	2	1	0	1	29 (23–34)
Infection	3	2	1	0	23 (23–25)
Chromosome	9	8	1	0	20 (15–28)
Unidentified	31	25	5	1	20 (15–32)
Total	91	74	10	7	22 (15–36)

(27.9%) resulted in intrauterine fetal death (IUFD), and 31 (72.1%) survived to birth. Of these 31 infants, 19 had early neonatal death, 2 had late neonatal death, and 10 survived to 1 year of age. Early neonatal death occurred in 46% and 54% of the cases with cardiac abnormality and unidentified etiology, respectively. All late neonatal deaths were observed in cases with unidentified etiology. The ratio of termination was detected significantly higher in the known etiology group (65% vs. 29%) (p=0.001; p<0.05). However, there was no significant difference between groups in terms of IUFD ratio (33.3% vs. 22.7%) (p=0.438; p>0.05), neonatal death (33.3% vs. 63.6%), and survival (33.3% vs. 13.6%) (p>0.05). The ratio of TOP was detected significantly higher in the known etiology group (65% vs. 29%) (p=0.001; p<0.05). However, there was no significant difference between groups in terms of IUFD (33.3% vs. 22.7%) (p=0.438; p>0.05) and neonatal death (50% vs. 82.4%) (p=0.055; p>0.05). Comparison of outcomes among cases with known and unknown etiology is shown at Table 4.

Table 5 shows perinatal and postnatal outcomes of the remaining 43 cases, after exclusion of the terminated cases, according to their gestational age at diagnosis. Of the 26 patients diagnosed with NIHF before 24 weeks of gestation, 8 (30.7%) developed IUFD, and 2 survived to 1 year of age. Of the ten patients diagnosed with NIHF between 24 and 28 weeks of gestation, 3 (30%) developed IUFD, and 4 survived to 1 year of age. In addition, of the 7 cases diagnosed after 28 weeks of gestation, only one developed IUFD, and 4 (57%) survived to 1 year after delivery.

The survival rate at discharge was 23.2% (10 out of 43) in cases who elected to continue with their pregnancy. Table 6 summarizes the clinical details of the ten survivors. Of these 10 cases, seven had an identified etiology. The remaining 3 cases could not be determined despite many postnatal examinations. Cardiac etiology was identified in 2 cases, one of which had fetal therapy with digoxin and sotalol due to supraventricular tachyarrhythmia and the other of which had non-compaction cardiomyopathy. Intrauterine perforation of Meckel's diverticulum was diagnosed postnatally in one case. Fetal anemia was detected in 2 cases; one of them was due to Parvovirus infection; however, the etiology of fetal anemia could not be identified in the other case. None of the cases required intrauterine transfusion due to spontaneous resolution of hydrops in one case with Parvovirus infection. The other case with anemia was delivered

Table 4: Comparison of outcomes among cases with known and unknown etiology

	Known etiology		Unkown etiology		p
	n	%	n	%	
TOP					0.001[1]*
Yes	39	65	9	29	
No	21	35	22	71	
Outcomes					0.438[1]
IUFD	7	33.3	5	22.7	
Live birth	14	66.7	17	77.3	
Outcomes					0.055[1]
Neonatal death	7	50	14	82.4	
Survival	7	50	3	17.6	

TOP: Termination of pregnancy; IUFD: Intrauterine fetal death; *: P<0.05; 1: Chi-square test.

Table 5: Perinatal and postnatal outcomes of 43 cases after exclusion of terminated cases

Gestational age at diagnosis	IUFD	Early neonatal death	Late neonatal death	Survival at 1 year	Total
<24 gestational week	8	14	2	2	26
24–28 gestational week	3	3	0	4	10
>28 gestational week	1	2	0	4	7

IUFD: Intrauterine fetal death.

Table 6: Clinical details of the surviving patients

Gestational age at diagnosis	Etiology	Delivery week	Birthweight (gr)	Fluid accumulation	Outcome
25	Unidentified	38	2290	As/Sc	Hydrops completely regressed at 29 weeks
26	Unidentified	39	2960	As/Sc	Minimal ascites at birth
25	Unidentified	38	3600	As/Sc/Plv	Hydrops completely regressed at 32 weeks
29	Cardiac	38	3400	As/Plv/Per	SVT and hydrops regressed at 34 weeks with fetal therapy
29	Cardiac	31	1527	Plv/ Sc/ As	Cardiomyopathy and postnatal respiratory support at NICU
33	Gastrointestinal	35	2935	As/Sc/Plv	Intrauterine perforation of Meckel's diverticulum
23	Infection	38	3150	Asc/per	Parvovirus at amniocentesis Spontaneously regressed at 24 weeks
35	Anemia	35	2930	Asc/Plv/Sc	Unidentified anemia postnatally
21	Chromosome	36	3130	Plv/Sc	Trisomy 21 at amniocentesis Died at 4 years old
26	Cystic hygroma	36	2670	Plv/sc	Hydrops completely regressed at 32 weeks

Asc: Ascites; Plv: Pleural effusion; Sc: Skin/scalp edema; Per: Pericardial effusion; SVT: Supraventricular tachyarrhythmia.

due to advanced gestational week. One case with trisomy 21 survived to 4 years of age and died because of leukemia. The final case had cystic hygroma and hydrops which completely regressed at 32 weeks of gestation. Hydrops was observed to regress completely in 9 out of 10 cases during follow-up.

DISCUSSION

In our series, the causes of NIHF were prenatally identified in 65.9% of the cases but the most common cause of NIHF remained as "etiologically unidentified" or "idiopathic" in 34% of the cases. Similarly, Gilby et al.[3] reported that the largest etiological group consisted of idiopathic cases with a rate of 31% out of 131 cases in their study. In addition, Hasnani-Samnani et al.[4] could not report a definitive cause for 42% of their patients with NIHF. Bellini et al.[5] provided the most extensive and detailed overview of NIHF causes. In their study, they systematically reviewed 56 articles in 2009, and later they updated their study with additional 24 articles in 2015. They reported that cardiovascular (20%) and idiopathic (19.8%) causes were the most common underlying insults in NIHF.[6] Recently, Meng et al.[7] presented the largest report of underlying causes and outcomes of 1204 cases with NIHF in Southern China. They reported that causes of NIHF could be identified prenatally in 72.0% of cases and the most common diagnoses were hematologic diseases (28.4%) and chromosomal abnormalities (19.8%). In the literature, the percentage of idiopathic causes varies according to the diagnostic methods that are used in each clinic. In the current study, most of the parents refused karyotype analysis (54%) and postmortem autopsy (80.2%), so some abnormal karyotypes and additional structural abnormalities might have been underestimated. In their prospective series of 53 consecutive cases, Moreno et al.[8] were able to make a diagnosis in 87% of cases including a metabolic disease (nearly 6%) using an expanded protocol. In addition, Takci et al.[9] from Turkey reported that 9% of infants with NIHF had inborn errors of metabolism. This was probably due to the high frequency of consanguineous marriages in Türkiye. Current data are from 6 to 13 years ago, and there have been changes in the management of the disease since then. Among these major changes in the management of NIHF are the types of genetic testing for the investigation of the etiology. Genetic testing is used to identify pathogenic changes in NIHF, and it varies from standard karyotype analysis and chromosomal microarray analysis (CMA) to gene panels and broad approaches such as

whole-exome sequencing (WES). Although CMA was recommended in place of karyotype analysis for the diagnosis of fetal anomalies, limited data have been published on the success of CMA for NIHF. In addition, WES is also not clearly defined for its use in investigating the abnormalities beyond the standard genetic workup.[10] In 2015, the Society for Maternal-Fetal Medicine published an algorithm for the evaluation of NIHF and recommended the consideration of more targeted testing such as lysosomal enzyme assays for cases of a structurally normal fetus with negative genetic test results.[11] The percentage of idiopathic cases seemed to decrease after complete investigation but the required analyses such as CMA, WES, and metabolic testing were not available in our institution to achieve a complete evaluation before 2015.

It is important to diagnose potentially treatable conditions, to rule out disorders with a risk of recurrence, to offer termination to those with lethal prognosis, and to inform the patients about the uncertain prognosis of idiopathic cases. After intensive counseling, 52.7% of the cases elected termination of pregnancy. None of the cases with lethal thoracic, genitourinary, skeletal abnormalities, genetic syndromes, and fetal tumor elected to continue with their pregnancy. Patients with uncertain prognoses such as cardiac abnormality and the patients in the unidentified group had the lowest termination rates of 18.7% and 29%, respectively. In the current study, the determination of the etiology seems to affect the termination of pregnancy rate but not in terms of IUFD, neonatal death, and survival. Although this cohort is relatively large compared to other published series, the heterogeneity of the underlying causes and the relatively low number of cases in most of the diagnostic groups (thoracic, genitourinary, skeletal abnormalities, genetic syndromes, and fetal tumor) limit the comparison of the outcomes between subgroups for statistical analyses.

The outcome of NIHF cases remains poor despite the advances in diagnosis and neonatal management. In the current study, the overall survival to hospital discharge rate for the fetuses was 11% (10 out of 91 cases) after a diagnosis of NIHF. After the exclusion of the terminated cases, of the remaining 43 cases, 12 (27.9%) resulted in IUFD, and the remaining 31 (72.1%) survived to birth. The survival rate at discharge was 23.2% (10 of 43 cases). In 2011, Santo et al.[12] performed a literature review of five prenatal studies which were published between 1999 and 2009. In their study, the rates of survival beyond 28 days were varying between 8.6% and 48% in 297 patients that included terminated cases. More recent studies have reported that the survival rate after the exclusion of the terminated cases was between 27% and 44%, and the survival rate of live born infants was between 57% and 73%.[13,14] Ota et al.[15] carried out a study of 92 cases, 41 (45%) of which resulted in fetal death and 33 (36%) survived to 1 year. The survival rate in the present study was better than the rates in previous studies which were conducted in the 1990s, and it may be due to the improvement of neonatal and fetal therapies.

The present study showed that spontaneous resolution and favorable prognosis could be observed in conditions like cardiac arrhythmia, Parvovirus B 19 infection and if the onset of hydrops was after 24 weeks of gestation. In our study, hydrops in 9 of 43 (21%) fetuses completely resolved prior to birth. All these infants survived. Among the survived fetuses, only one had minimal ascites of undefined etiology at birth. In the present study, none of the hydropic fetuses survived at birth. Our results were consistent with those of Derderian et al.[16] and Gilby et al.[3] who reported higher survival rates in hydropic infants whose conditions had resolved prior to birth. Although Gilby et al.[3] revealed that in the fetuses with persisting hydrops and who remained hydropic at the time of birth, survival decreases further to 40%, and no other study has reported a survival rate for live born infants that are still hydropic at birth. Derderian et al.[16] reported a survival rate of 76% in cases with an antenatal resolution rate of 32% and when compared, the survival rate in cases without antenatal resolution was 33%.

In our 43 cases, the group of patients who were diagnosed with hydrops after 24 weeks had more live births, less fetal demise, and a higher postnatal survival rate compared to the group of those who were diagnosed before 24 weeks. Unfortunately, this comparison cannot be conclusive due to the small sample size. Survival to discharge rates before and after 24 weeks was 7.7% and 47%, respectively. Similarly, Ota et al.[15] reported that intact survival rates in NIHF that were diagnosed before 22 weeks, between 22 and 25 weeks, between 26 and 29 weeks, and after 30 weeks were 12%, 5%, 23%, and 26%, respectively. The current study may show that gestational age at diagnosis correlates with the prognosis of NIHF. In contrast to our study, Hasnani-Samnani et al.[4] reported higher postnatal survival rates (80% vs. 50%) in cases who were diagnosed before 24 weeks of gestation. Czernik et al.[17] revealed no difference in survivors and non-survivors with regard to gestational age at diagnosis and time interval between diagnosis and delivery in their study of 70 live-born HF infants. Therefore, patients should be counseled about uncertain prognoses regardless of whether NIHF is diagnosed in the first or second half of pregnancy.

Cardiac anomalies were the most commonly detectable abnormality in the study. Most of the cases with cardiac structural abnormality developed IUFD or early neonatal death. Although the mortality rate of fetal hydrops due to cardiac reasons is generally high, some disorders can be treated by fetal therapy and result in the reversal of hydrops and improved survival rates. One case with fetal tachyarrhythmia was effectively treated with transplacental antiarrhythmic drugs. Fetal anemia is another treatable cause of NIHF. However, in the present study, intrauterine blood transfusion was not performed in one case of NIHF with Parvovirus infection due to the spontaneous resolution of fetal hydrops in the subsequent week. The second case of anemia with unknown etiology was delivered because the patient was at 35 weeks of gestation. Despite the improvement in the outcome of NIHF due to viral infection, fetal anemia, and fetal arrhythmia along with the progress in fetal diagnosis and therapy, the impact of other prenatal interventions on perinatal mortality in fetuses with idiopathic NIHF is controversial.[18] In a study by Nassr et al.,[19] among the 54 fetuses with idiopathic NIHF, 12 had fetal interventions, such as thoracoamniotic shunt placement and paracentesis while 42 were treated expectantly. Subgroup analysis of hydropic fetuses with pleural effusion showed no differences regarding neonatal mortality and survival to discharge rates between the cases who underwent fetal intervention and those who did not undergo.[19] Although some groups showed improvement in survival rates with fetal interventions in a heterogeneous population of hydropic fetuses with pleural effusion, further systematic researches are needed to determine the impact of prenatal interventions on perinatal mortality in fetuses with idiopathic NIHF.[20]

The first limitation of the study was its retrospective design. The second limitation is that a complete investigation could not be done for all patients in our study, thus a thorough diagnostic protocol might have identified more causes of NIHF. Despite being valuable tools that confirm the diagnosis and reveal the new findings, karyotyping was performed in almost half of the cases, and an autopsy was performed in a minority of cases. In addition, CMA, as well as WES, could not be performed in any of the cases because of the limited resources of our institution. No metabolic or placental disease (e.g., syphilis) was identified among the cases due to incomplete evaluation which is also reflected by the relatively high number of etiologically unidentified cases. The long-term outcome is one of the most valuable data, but we could not obtain this data which shows long-term neurological outcomes in survived patients. The strength of our prenatal cohort study is its large sample size which reflects a proportion of prenatal abnormalities in the Turkish population, so it can provide the clinicians data for them to counsel the affected families.

CONCLUSION

NIHF is still a complex problem and mortality rates remain high despite advances in fetal and neonatal treatment. Recent data on the outcomes of NIHF are still limited to help the clinicians to provide the exact data to the affected families on the prognosis of the complex pregnancies.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital University Clinical Research Ethics Committee granted approval for this study (date: 15.08.2014, number: 143).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – EE, RA; Design – EE, RA; Supervision – EE; Resource – SS, OP, MM; Materials – OP, MM; Data Collection and/or Processing – EE, SS; Analysis and/or Interpretation – SAA; Literature Search – FK; Writing – EE, LU; Critical Reviews – EE, LU.

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