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RESEARCH ARTICLE

A Retrospective Analysis of Cases of Non-Immune Hydrops Fetalis in A Tertiary Center

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Abstract

Introduction: Non-immune hydrops fetalis (NIHF) can occur at different gestational ages and with different etiologies. The aim of this study was to investigate the association of gestational age at diagnosis and a novel clinical scoring system with survival in NIHF cases **Methods:** This retrospective study was conducted between January 2020 and January 2023 in the perinatology clinic of a tertiary care center. Maternal characteristics, causes of NIHF, and survival rate were analyzed. The hydrops score was calculated and compared for those less than and greater than 20 weeks. **Results:** Of 41 NIHF, etiology was determined in 76% (87% <20 weeks vs. 70% ≥20 weeks), including cardiovascular malformations (27%), cystic hygromas (17%), and chromosomal defects (12%). Cystic hygromas were more common before 20 weeks. Cardiac malformations were the most common cause after 20 weeks. There was a negative correlation between live birth and hydrops score. The overall survival was 7.3%. The most favorable overall survival is in NIHF cases associated with fetal arrhythmias and placental pathology for the second and third trimesters, respectively. **Conclusion:** Earlier gestational age at diagnosis and higher hydrops score are associated with lower survival rates in NIHF cases. Determining the cause, accompanying structural abnormalities, and the week NIHF is diagnosed will help predict prognosis and apply treatments earlier to improve care for these fetuses and newborns

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Introduction

Non-immune hydrops fetalis (NIHF) is a complex condition defined as excessive fluid accumulation in two or more fetal compartments, such as skin, pleura, pericardium or peritoneum, and placenta.[1] NIHF occurs in 1 in 2000-3500 live births. A heterogeneous group of conditions, including hematologic, cardiovascular, chromosomal, infectious, syndromic, thoracic, and idiopathic, can cause NIHF.

The Maternal-Fetal Medicine Society has developed recommendations for evaluating the hydropic fetus, including maternal blood tests, comprehensive ultrasonography of the fetus and placenta, fetal echocardiography, middle cerebral artery doppler studies, and a fetal karyotype.[2] Cases of aneuploidy can be diagnosed by karyotype or chromosomal microarray analysis; however, in some cases, the etiology remains unclear even after standard testing.[3] If necessary, more specialized tests should be recommended. Despite extensive investigation, the cause of 15-25% of NIHF cases is unclear—the causes of hydrops influence overall morbidity and mortality.[4] Identifying NIHF-related causes is critical for prenatal counseling and managing subsequent pregnancies.

This study aims to determine the etiology and outcome of NIHF concerning gestational age at diagnosis in the prenatal period.

Material and Methods

This retrospective study was conducted between January 2020 and January 2023 in the perinatology clinic of a tertiary care center. Medical records of all cases diagnosed with NIHF were analyzed. Consent for data and image recording was obtained from all patients, the Ethics Committee approved the study, and the Declaration of Helsinki was followed (E2-23-3837).

Fetal hydrops was defined as cystic hygroma or excessive fluid accumulation in more than two fetal body cavities. Cases with hydrops due to isoimmunization were excluded from the study, and patients diagnosed with NIHF at any week of gestation were included. Karyotype analysis was performed in patients who accepted chorionic villus sampling, amniocentesis, or cordocentesis. Patients were screened prenatally for anatomic malformations that could cause hydrops, antibodies to red blood cells, peak systolic middle cerebral artery velocity, and maternal infections (cytomegalovirus, toxoplasmosis, syphilis, parvovirus B19). Each patient underwent a comprehensive sonographic examination according to gestational age. Fetuses with increased nuchal translucency (NT) and cystic hygromas were included in the study between 11-13+6 weeks of gestation. The compartments of fluid accumulation, concomitant fetal anomalies, and fetal anemia findings were assessed. Abnormal NT was defined as > 95% percentile for crown-rump length. Maternal characteristics, serologic results, sonographic findings, pregnancy outcomes, survival rates, stillbirths, or neonatal deaths were recorded. The possible etiologic causes of NIHF were classified, and the causes were identified before and after 20 weeks of gestation. The hydrops fetalis score was calculated using information obtained by fetal ultrasound and doppler examination, and its association with survival was analyzed between the live birth group and the group of intrauterine exitus or termination of pregnancy (TOP). Five parameters were evaluated: (1) Maternal age, <35, ≥35 (2) Gestational age at diagnosis <20, ≥20 weeks (3) Fetal hydrops components, pleural effusion, abdominal assit, cystic hygroma (4) Doppler flow velocimetry of the ductus venosus (5) Cardiac function: Tricuspid regurgitation, mitral regurgitation, arrhythmia, major cardiac anomaly (Table 1).

SPSS version 22.0 software (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. Descriptive data were expressed as frequencies and percentages. Pearson's chi-square and Fisher's exact tests were used to analyse categorical data. The "independent sample t" test was used to compare the measurements of two groups when normally distributed. The "Pearson" correlation coefficient was used to examine the relationship between groups. A p-value of less than 0.05 was considered statistically significant.

Table 1. Parameters used in hydrops scoring

Maternal age (years)	**Gestational age of diagnosis (weeks)**	**Hydrops compartment**	**Ductus venosus doppler**	**Cardiac function**
<35: 0 ≥35: 1	<20: 1 ≥20: 0	Cystic hygroma: 1 Pleural effusion: 1 Abdominal ascites: 1 Skin edema: 0	Normal: 0 Reverse: 1	Tricuspid regurgitation: 1 Mitral regurgitation: 0 Arrhythmia:1 Major cardiac anomaly: 1

Results

Forty-one pregnancies with NIHF were analyzed. The mean maternal age was 31.5 years (24-44 years), and the mean gestational age at the initial

diagnosis was 22 weeks (11-34 gestational weeks). The etiology of NIHF could be determined in 76% (n=31) of cases, while it remained undetermined in the remaining 24% (n=10) cases. The most common condition associated with NIHF was cardiovascular malformations (11 cases, 27%), followed by cystic hygromas (7 cases, 17%) and chromosomal defects (5 cases, 12%). Subgroup analysis revealed that gestational age was less than 20 weeks in 17 cases and between 20 and 40 weeks in 24 cases. Chromosomal abnormalities and cystic hygromas occurred more frequently before 20 weeks gestation, whereas cardiac malformations were the most common cause after 20 weeks. The rate of cystic hygromas was statistically significantly higher before 20 weeks of gestation than after 20 weeks (Table 2). Hypoplastic left heart syndrome (HLHS) (27%) was the most common cardiovascular malformation, followed by pulmonary atresia with ventricular septal defect (18%) and pulmonary hypoplasia (18%) (Table 3). Chromosomal abnormalities detected at NIHF included trisomy 21, trisomy 18, trisomy 13, Turner syndrome, and triploidy (Table 4).

Table 2. Analysis of Non-Immune Hydrops Fetalis Based on Gestational Age

Parameters	<20 week (n=15)	20-40 week (n=26)	p-value
Congenital Cardiac defects	2	9	0.04
Chromosomal abnormality	4	1	0.06
Cystic hygroma	6	1	0.00
Skeletal dysplasia	0	2	0.22
Cardiac tumor	0	1	0.39
Cardiac arrhythmia	0	3	0.66
Placental chorioangioma	0	1	0.39
Partial molar pregnancy	1	0	0.18
Idiopathic	2	8	0.17
Live birth	0 (0%)	14 (53.8%)	0.00

p-value <0.05 was considered statistically significant.

Table 3. Cardiovascular Causes of Non-Immune Hydrops Fetalis

Cardiac anomaly	Number of cases, n	Percentage
Hypoplastic left heart syndrome	3	27%
Pulmonary hypoplasia	2	18%
Pulmonary atresia with ventricular septal defect	2	18%
Tetralogy of fallot	1	9%
Critical aortic stenosis	1	9%
Hypoplastic right ventricle	1	9%
Tricuspid atresia and pulmonary atresia	1	9%

Table 4. Chromosomal abnormalities

	Number of cases, n
Trisomy 21	1
Turner syndrome	1
Triploidy	1
Trisomy 18	1
Trisomy 13	1

Fourteen infants were born alive (34%), and three infants were discharged alive from the hospital. The overall survival rate was 7.3%. The defined etiology of hydrops in the surviving fetuses was placental chorioangioma, fetal supraventricular tachycardia, and idiopathic cause. The mean hydrops score of the group with intrauterine exitus or TOP was significantly higher than the live birth group (4.4±1.0 vs. 3.6±1.2 p=0.04). Correlation analysis showed a weak negative correlation between live birth and hydrops score (r=0.30, p=0.06). In the group that died after birth, median survival ranged from 60 minutes to 51 days. Live-born cases are shown in Table 5.

Table 5. Live Born Cases with Non-Immune Hydrops Fetalis

	Gestational age at diagnosis of NIHF (weeks)	Gestational age at birth (weeks)	Weight (g)	Gender	Survival time	Etiology
1	22	30	2450	M	31 day	Fetal arrhythmia (atrioventricular block)
2	26	32	2710	M	3 hour	Skeletal dysplasia
3	23	27	1550	M	21 day	Fetal arrhythmia (supraventricular tachycardia)
4	26	29	1820	M	1 hour	Idiopathic
5	28	31	1770	F	Healthy	Placental chorangioma
6	28/4	33/4	2100	F	51 day	Cardiac anomaly (Tetrology of fallot)
7	34/4	37	2560	F	Healthy	Idiopathic
8	25	25/5	1540	M	9 hour	Cardiac anomaly (Aortic stenosis)
9	21/5	29/2	1500	F	5 hour	Cardiac anomaly (Hypoplastic right heart syndrome)
10	32/4	38	3060	F	3 hour	Skelatal dysplasia
11	24	30	1500	F	1 hour	Cardiac anomaly (Pulmonary and tricuspid atresia)
12	22	35	2260	F	Healthy	Fetal arrhythmia (Supraventricular tachycardia)
13	31	32	2850	M	1 hour	Cardiac anomaly (Pulmonary hypoplasia)
14	30	34	2250	M	2 hour	Idiopathic

F, female; M, male.

Discussion

In this study, the causes of prenatally diagnosed cases of NIHF were investigated and classified according to gestational age. Our results suggest that the leading cause of NIHF after 20 weeks of gestation

is cardiovascular abnormalities, with HLHS being the most common cause. The etiology can be identified in up to 80% of prenatally diagnosed NIHF cases, with the most favorable overall survival in NIHF associated with fetal arrhythmias and placental chorioangiomas. NIHF is caused by several etiologic variables that may be maternal, fetal, or placental. Impaired vascular permeability, lymphatic drainage due to changes in osmotic pressure, and impaired venous pressure balance are the physiologic factors that cause NIHF.5 The etiology can be determined in 60-85% of cases prenatally or postnatally.[6] The remaining cases are considered idiopathic (i.e., no prenatal or postnatal anatomic malformations were detected, no maternal antibodies to red blood cells, normal peak systolic velocity in a middle cerebral artery, no known monogenetic disorders, fetal tumors, and negative screening for maternal infections (e.g., cytomegalovirus, toxoplasmosis, syphilis, parvovirus B19), euploid fetal karyotype.[6],[7] Cardiac etiologies of hydrops fetalis account for 10-20% of diagnosed NIHF in the prenatal period, including structural cardiac abnormalities, arrhythmias, cardiac tumors, and cardiomyopathy.[8] In our study, cardiac causes of NIHF accounted for 39% of all etiologic causes. Of these, 75% (n=11) were cardiac malformations, 19% (n=3) were cardiac arrhythmias, and 6% (n=1) were NIHF due to cardiac tumors. Cardiac malformations can be simple or complex.[9],[10] Our study found that the most common cardiac abnormality causing hydrops was HLHS. The two leading causes of hydrops fetalis are hemodynamic changes and conduction abnormalities associated with congenital structural heart defects. These congenital structural heart anomalies have been associated with significant left heart problems, such as HLHS, often associated with a narrowed foramen ovale, massive atrioventricular defect, and severe aortic stenosis. Because HLHS with normal venous Doppler measurements and normal cardiovascular function has a low risk of fetal death in utero.[11]-[13] According to some authors, the most common cause of NIHF is a right heart defect causing increased pressure and venous volume overload.[14] Another explanation for NIHF in HLHS is outflow obstruction due to severe aortic stenosis, which can lead to myocardial dysfunction of the left ventricle. The excess volume then causes dysfunction of the right ventricle, leading to intrauterine heart failure, which manifests as hydrops fetalis.[15],[16] A case of HLHS with concomitant hydrops has been described in the literature as tricuspid stenosis characterized by increased central venous pressure and abnormal venous Doppler measurement leading to fetal hydrops.[17] This fetus has significant atrial systolic flow reversals in the ductus venosus and pulsatility in the umbilical vein. Such reversals in the fetus indicate high central venous pressures.[18],[19] In our study, two cases of HLHS were associated with severe mitral and aortic hypoplasia, and one HLHS case was associated with Turner syndrome, which has an abnormal lymphatic system circulation. One of the most common causes of NIHF is cardiac arrhythmias. Fetal tachyarrhythmias such as supraventricular tachycardia (SVT) result in increased atrial pressure and decreased cardiac output, leading to heart failure. Based on pathogenesis, arrhythmias are the most treatable cardiac causes of hydrops fetalis.[20] Severe bradyarrhythmias accompanied by SVT and complete heart block are common and serious fetal arrhythmias. Hydrops fetalis may be caused by a congenital atrioventricular heart block, which has been shown to respond effectively to transplacental treatment or direct fetal therapy.[21] Our study found cardiac arrhythmias in 3 fetal hydrops, including SVT in 2 fetuses, and congenital complete AV block in 1 fetus. Despite intrauterine salbutamol treatment in a fetus with complete AV block, no improvement was noted, and birth occurred in the 30th week. A pacemaker was implanted in the newborn after birth, and died on postnatal day 31 due to cardiac arrest. Intrauterine digoxin treatment was initiated in two fetuses diagnosed with SVT. In both cases, SVT improved one day after treatment. One of the two fetuses was delivered at 27 weeks gestation because of fetal distress, and at the third week after birth, the fetus died because of systolic dysfunction. Hydrops and SVT attacks of the other fetus improved with antiarrhythmic treatment in the postnatal period, and the newborn was discharged with medication. Cardiac tumors also can cause NIHF by causing cardiac arrhythmias and obstruction of vascular outflow.[22] In a retrospective analysis, 84 cases of fetal tumors were studied. Cardiac tumors accounted for 23.8%, causing arrhythmias in 42% of cases.[23] In our study, patient with fetal cardiac tumor preferred to terminate pregnancy in an external center at 19 weeks of gestation. NIHF occurs in approximately 5-6% of cases with lymphatic dysplasia 2. Increased nuchal translucency, cystic hygromas, and chylothorax are common in Turner syndrome, especially in the first trimester, but also occur in other genetic syndromes such as mul-

tiple pterygium syndrome and RASopathies such as Noonan syndrome.[24] In our study, 17% of cases were found to have cystic hygroma. These cases were mostly observed in the first trimester, which was statistically significant.[25] Genetic examinations such as karyotyping and microarray analysis are the recommended first-line tests for NIHF cases. They can detect 7-17% of NIHF cases due to chromosomal abnormalities and copy number variants.[3],[25] However, microarray analysis cannot be routinely performed in our country due to its high cost. Trisomy 21, trisomy 18, trisomy 13, triploidy, and Turner syndrome were detected in a small group of patients who requested karyotype analysis. Placental pathologies should also be considered as potential etiologies of NIHF. Chorioangioma, umbilical cord angiomyxoma, and umbilical artery aneurysm are rare diseases of the placenta and umbilical cord associated with NIHF.2 It is unclear in which trimester NIHF due to placental pathology is more frequent, but the extent of pathology influences the week of hydrops formation. Large placental chorangiomas (> 5 cm) are likely to result in rapid NIHF due to high-output heart failure.[2] In our study, NIHF cases occurred in the first trimester due to partial mole and in the second trimester due to chorangioma. One of the surviving fetuses in our study was hydrops due to placental chorioangioma. The blood supply of the chorioangioma was destroyed by diode laser coagulation at 28 weeks of gestation. After the procedure, fetal hydrops improved, and delivery occurred at 32 weeks of gestation. A healthy infant is in follow-up. Once the NIHF etiology is determined, hydrops scoring can help interpret the prognosis. The hydrops scoring parameters in our study were partially similar to the few studies in the literature. We found a significantly lower hydrops score in the live birth group and a negative correlation between hydrops score and fetal outcome. In the literature, the proportion of idiopathic etiology in NIHF cases varies, with about one-third classified as idiopathic. Prenatal examinations contributed to the increase in etiology detection rates. Definitive diagnoses are more common in early gestation. A previous study found that 83.3% of 19 cases with NIHF in the first trimester were associated with structural abnormalities and 47.3% with chromosomal abnormalities.[26] In our study, 13% of NIHF cases were idiopathic before 20 weeks, whereas this rate was 30% after 20 weeks. In some cases, an autopsy may help determine the underlying cause. A significant limitation of our study is that most patients did not undergo genetic testing or fetal/neonatal autopsy, so these cases were described as idiopathic. One of the advantages of our study is that we have investigated and described in detail the etiology of NIHF in a tertiary center with a large number of cases. Although several etiologic causes have been identified, the survival rate in NIHF is very low because of limited treatment options. The overall survival rate was 7.3%. Median survival in the group that died after birth ranged from 60 minutes to 51 days.

Conclusion

NIHF is caused by a heterogeneous group of underlying diseases. Cardiovascular abnormalities are the main cause of NIHF after the mid-trimester. The prognosis of NIHF cases diagnosed in the first trimester is very poor, and the survival rate of NIHF due to fetal arrhythmias and placental abnormalities in advanced weeks of gestation is relatively high. Determining the cause, accompanying structural abnormalities and the week NIHF is diagnosed will help predict prognosis and apply earlier treatments to improve care for these fetuses and newborns.

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Conflict of interest
The authors report there are no competing interests to declare

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