Non-immune fetal hydrops: etiology and outcomes according to gestational age at diagnosis

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CONTRIBUTION

What are the novel findings of this work?

Nonimmune fetal hydrops (NIFH) has significantly different etiologies according to the trimester of diagnosis.

NIFH diagnosed in the first trimester is associated with an increased risk of aneuploidy and higher risk of perinatal loss; the etiology remains unknown in at least one third of the cases of NIFH diagnosed in second and third trimester.

What are the clinical implications of this work?

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NIFH is a severe condition with a guarded prognosis. Gestational age at diagnosis is a crucial aspect of counseling: pregnancy outcomes significantly differed across trimesters, with higher livebirth rates when NIFH was diagnosed later in pregnancy. Fetal therapy, although not resolving the condition itself, was associated with improved survival.

ABSTRACT

Objectives: Fetal hydrops is associated with increased perinatal mortality and morbidity. The etiology and outcomes of fetal hydrops may differ according to the gestational age (GA) at diagnosis. The aim of this study was to evaluate the causes, evolution and outcomes of non-immune fetal hydrops (NIFH) according to the GA at diagnosis.

Methods: This was a retrospective cohort study of all singleton pregnancies complicated by NIFH at the Fetal Medicine Unit at St George's University Hospital, London between 2000 and 2018. All fetuses had a detailed anomaly and cardiac ultrasound scans, karyotyping and infection screening. Prenatal diagnostic and therapeutic interventions, GA at diagnosis and delivery, as well as pregnancy outcomes were recorded. Regression analysis was used to test for potential association between possible risk factors and perinatal mortality.

Results: We included 273 fetuses with NIFH. Etiologies varied significantly in the three trimesters. Excluding women declining invasive testing (n=30), the cause of NIFH was defined as "unknown" in 62 out of 243 cases (25.5%). Chromosomal aneuploidy was the commonest cause in the first trimester. It continued to be a significant etiologic factor in the second trimester along with congenital infections. In the third trimester, the most common etiology was cardiovascular abnormalities. Among the 152 (55.7%) women continuing the pregnancy, 48 (31.6%) had fetal intervention, including the insertion of pleuro-amniotic shunts, fetal blood transfusion and thoracocentesis. Fetal intervention was significantly associated with lower perinatal mortality (OR 0.30, 95% CI 0.14-0.61, p<0.001); this was confirmed also after excluding cases with a diagnosis of anemia or infections (OR 0.29, 95% CI 0.13-0.66, p=0.003). In fetuses not undergoing active fetal intervention (n=104), the GA at diagnosis was the only parameter which was significantly associated with the risk of perinatal mortality (OR=0.92, 95%CI: 0.85 to 0.99, p=0.035), while the body cavity involved and polyhydramnios were not (p >0.05).

Conclusions: Earlier GA at diagnosis was associated with an increased risk of aneuploidy and worse pregnancy outcomes, including higher risk of perinatal loss. Fetal therapy was significantly associated with lower perinatal mortality.

Introduction

Despite advances in fetal medicine, the perinatal mortality in Fetal Hydrops (FH) remains high. FH is a pathologic condition characterized by deranged fluid homeostasis leading to abnormal fluid accumulation in fetal interstitial spaces. (1,2) It is traditionally detected by ultrasound and defined as the presence of fluid in two or more fetal serous cavities, including skin oedema, ascites, pleural and/or pericardial effusion. (3) Historically, most cases of FH were caused by red-cell alloimmunization and defined as immune hydrops fetalis (IFH). Thanks to the introduction and widespread use of Rhesus (D) immune globulin, non-immune fetal hydrops (NIFH) accounts now for almost 90% cases of hydrops with a reported prevalence of 1 in 1700-3000 pregnancies. (3-7)

NIFH can be caused by a large number of underlining pathologies, all leading to an imbalance in the regulation of fluid movement between the vascular and interstitial spaces, with an increase in interstitial fluid production or a decrease in lymphatic return (3, 8). The most frequent etiologies of NIFH in prenatally diagnosed cases, as described by Santo et al., were aneuploidy (19%), cardiovascular abnormalities (15%), infections (14%) and thoracic disorders (12%). (9) Other conditions associated with NIFH include "syndromic", single-gene and metabolic disorders, twin-twin transfusion syndrome, congenital infection, placental abnormalities and fetal tumors. (3)

Previous studies do not enable us to provide individualised assessment and counselling as most of them have not stratified the results according to the gestational age (GA) at diagnosis or prenatal active fetal intervention (8-13). Therefore, we aimed to investigate the aetiology, evolution and outcomes of NIFH according to GA at diagnosis and to determine the factors which influence the perinatal outcome in these pregnancies.

Material and Methods

We conducted a retrospective study of all cases of NIFH referred to our Fetal Medicine Unit at St. George's University Hospital, London, between 2000 and 2018. Our Fetal Medicine Unit is a tertiary referral centre for most fetal abnormalities in the region. NIFH was defined as the presence of fluid in at least two cavities including pericardial, pleural and abdominal effusions and/or skin oedema in the absence of atypical red cell antibodies. All fetuses underwent detailed structural and cardiac ultrasound examinations. Ultrasound scans were performed using ultrasound equipment consisting of 3–5 MHz convex sector probe and GE Voluson E8, GE Voluson E10, Toshiba Aplio, Aloka 4000 and Phillips iU22 ultrasound machines.

All pregnant women were offered fetal karyotyping, maternal infection screening (toxoplasmosis, cytomegalovirus [CMV] and parvovirus B19 and others depending on the relevant history) and Kleihauer-Betke testing. Rubella immunological serology, treponemal screening and maternal haemoglobin electrophoresis were ascertained from maternal records as part of booking maternal investigations, which are usually conducted in the first trimester in all pregnant women in the UK. Detailed genetic testing including chromosomal micro-arrays (CMA) commenced in 2014, as well as gene panel testing and subsequently prenatal exome sequencing from 2018. We included all cases of NIFH irrespective of the GA at diagnosis. We excluded cases of hydrops in monochorionic twins due to twin-to-twin transfusion syndrome and those cases where the pregnancy outcome was not available.

We classified the aetiology of NIFH into nine main groups: chromosomal, single-gene disorders, , cardiovascular (structural, functional or rhythm) abnormality, other structural abnormalities, infection (parvovirus, CMV, toxoplasmosis, etc), placental chorioangioma, other causes and unknown etiology. Prenatal diagnostic and therapeutic interventions, termination of pregnancy (TOP) or GA at delivery and evolution of hydrops during pregnancy were recorded. We divided the pregnancies into three groups according to the GA at onset of NIFH, i.e. Group A up to 13+6 weeks, Group B from 14 to 24+6 weeks and Group C from 25 weeks onward. The reason why we chose to divide the Group B and C at 24-25 weeks was the option of termination still available as a choice for women till 24 weeks.

We also reviewed the detailed neonatal electronic records of the pregnancies with antenatal diagnosis of NIFH who were born after 2009, when a national mandatory neonatal electronic record had commenced, ascertaining data on the cause, treatment and length of stay at the neonatal unit.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and range. Binary and categorical variables were presented as the numbers and percentages. Distribution assumptions for continuous variables were visually assessed with quantile-quantile plots and then were confirmed with Shapiro-Wilk test. Continuous variables were compared using unpaired T-test or Mann Whitney test, while the Chi-square test was used for binary or categorical variables. Multivariate logistic regression model was fitted to test the effect of several prognostic factors such as GA at diagnosis, body cavity involved and the presence of concomitant polyhydramnios on the risk of perinatal mortality. A p-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics Version 21.

Results

Study population

NIFH was diagnosed in 279 fetuses between 2000 and 2018. Table 1 shows the general characteristics of our population. We included 6 (2.2%) fetuses from DCDA twin pregnancies. We present the data from twin pregnancies in Supplementary Table 1. The limited numbers do not allow any general conclusions; therefore, they were excluded from further analysis. We divided the remaining 273 patients into three different groups according to the GA at onset of NIFH, i.e. Group A up to 13+6 weeks (n=74), Group B from 14 to 24+6 weeks (n=117) and Group C from 25 weeks onward (n=82).

Etiological classification of NIFH

Table 2 presents the etiological classification of NIFH in singleton pregnancies according to the GA at diagnosis. The distribution of etiologies varied significantly in the three trimesters. Excluding women not having invasive testing (n=30, 11 in the first and second trimester, 8 in the third trimester) and where ultrasound failed to reveal an obvious identifiable etiology, the cause of NIFH was unknown in 62 out of 243 cases (25.5%).

In the first trimester (Group A), NIFH was due to chromosomal abnormalities in more than two thirds (69.8%) of the cases (44/63). Figure 1 shows the distribution of chromosomal abnormalities diagnosed. In Group B (14-24^{+6} weeks of gestation) 33/106 (31.1%) of NIFH were due to an unknown aetiology. Congenital infections were the second most common reason for NIFH in 19.8% (21/106) of the fetuses. The commonest infection was Parvovirus B19 affecting 17 (81%), while CMV and Toxoplasmosis affected 3 (14.2%) and 1 (4.8%) cases, respectively. Figure 2 shows the distribution of infective agents across all groups. In Group C (from 25 weeks onward), 23/74 (31.1%) cases had an unknown origin. Cardiovascular abnormality was the second most common cause of NIFH (17/74, 23%) with arrhythmia in 11/17 (64.7%) cases. Supplementary Table 2 shows the data in cases of unknown etiology diagnosed across all groups.

Pregnancy outcomes in NIFH

Termination of the pregnancy occurred in 121/273 (44.3%) of the included cases; 59 (79.7%), 53 (45.6%) and 9 (11%) cases in Group A, B and C respectively. Livebirth and IUD/miscarriage rates were significantly different according to the GA at the initial diagnosis, as shown in Table 3.

Among the 152/273 (55.7%) women continuing the pregnancy, 48/152 (31.6%) had fetal interventions (pleuroamniotic shunt (mono or bilateral),, intrauterine transfusion, thoracocentesis or paracentesis, intrauterine administration of digoxin through cordocentesis, interstitial laser for chorioangioma). Data regarding type of fetal intervention, etiology of NIFH and GA at diagnosis are presented in Supplementary Table 3. Congenital infection was significantly more frequent in the group which underwent fetal intevention (33.3% vs. 9.5%, p=0.007), as well as fetal anemia (14.3% vs 3%, p=0.002), while the other etiologies did not significantly differ between the two groups (Table 4) The two groups, i.e. fetal intervention vs. none, differed for mean GA at diagnosis (27.1 vs 23.4, p<0.001) and at birth (32.8 vs. 29.4, p=0.008), while there was no significant difference in the rate of resolved hydrops between the pregnancies which underwent fetal intervention (29.2%) and those which did not (19.2%), (OR 1.73, 95% confidence interval [CI] 0.78-3.81, p=0.17). However, we observed a significantly lower risk of perinatal death in those pregnancies which underwent fetal intervention (31.3% vs. 60.6%, OR 0.30, 95% CI 0.14-0.61, p<0.001).
In order to avoid the possible bias introduced by infections and anemia as treatable causes of NIFH and likely to be associated with good outcomes, we performed the same analysis after excluding infections and anemia from both groups. After excluding 12 cases of infections and 6 cases of anemia in fetal therapy group and 9 and 3 cases for infections and anemia respectively in no fetal therapy group, we still observed a significantly lower risk of perinatal death in those pregnancies that underwent fetal intervention (33.3% vs. 63.0%, OR 0.29, 95% CI 0.13-0.66, p=0.003).

Risk factors of perinatal mortality in NIFH

The multivariate logistic regression model evaluating the association between several prognostic factors such as GA at diagnosis, body cavity (skin, thorax, abdomen, pericardium) involved and the presence of concomitant polyhydramnios and the risk of perinatal mortality was performed in a cohort of fetuses with NIFH that did not receive fetal therapy (n=104). The GA at diagnosis was the only variable which was inversely associated with the risk of perinatal mortality (OR=0.92, 95% CI: 0.85

to 0.99, p=0.035). No significant association was observed with pleural effusion (OR=0.88, 95% CI: 0.35 to 2.19, p=0.780), pericardial effusion (OR=2.32, 95% CI: 0.87 to 6.19, p=0.090); ascites (OR=1.06, 95% CI: 0.39 to 2.93, p=0.910); skin oedema (OR=1.04, 95%CI: 0.41 to 2.62, p=0.940); cystic hygroma (OR=0.66 95%CI: 0.11 to 4.07, p=0.660) or polyhydramnios (OR=1.74, 95% CI: 0.54 to 5.6, p=0.230).

Discussion

Summary of study findings

The etiology of NIFH varied significantly in the three trimesters. Chromosomal abnormalities represent the most common etiology of NIFH in the first trimester, while the etiology remains unknown in at least one third of the cases later in pregnancy. Fetal intervention was significantly associated with lower perinatal mortality. In fetuses not undergoing active fetal intervention, the GA at diagnosis was the only parameter, which was significantly associated with the risk of perinatal mortality.

Interpretation of the findings and comparison with the published literature

Excluding 30/273 (11%) fetuses, whose karyotype was not available as the parents declined investigations and therefore aneuploidy or genetic cause could not be ruled out, the etiology of fetal hydrops could be identified in 181/243 (74.5%) of our study population. The proportion of cases receiving a definitive diagnosis is slightly smaller than that reported by published reviews of the literature (8, 10), so we reviewed the cases with unknown etiology looking for possible explanation. Among cases with "unknown diagnosis" (n=62/243), in 6/243 (2.5%) of the cases an abnormal posture of the fetus was noticed, suggesting a neuromuscular disorder, while in 8/243 (3.3%) a genetic cause was suspected but not identified, leaving the "real" idiopathic etiology to 48/243 (19.8%) of the study cohort, which is consistent with the published literature (Supplementary Table 2). (8).

Clinical and research implications

An important aspect in counselling the parents should be the GA at the initial diagnosis. As shown in this study, pregnancy outcomes significantly differ according to GA at the initial diagnosis, with higher livebirth rates when NIFH was diagnosed later in pregnancy. GA at diagnosis is probably related to the cause; aneuploidy being the commonest cause in the first trimester and thus influencing the prognosis. It is not surprising that almost 80% of women opted for termination of pregnancy (TOP) in the first trimester and more than one third of cases were terminated across gestation, since NIFH is a severe condition and is associated with guarded prognosis. Even excluding chromosomal abnormalities as a possible confounding factor influencing prognosis,

livebirth and IUD/miscarriage rates were significantly different according to the GA at the initial diagnosis (Supplementary Table 4). Survival was also influenced by fetal intervention. Although it did not necessarily resolve the hydrops itself, it was associated with improved survival; this was confirmed also after excluding fetuses with anemia and NIFH due to infections where a treatable /resolving cause is likely to be associated with good prognosis, increasing the strength of this observation.

The high proportion of cases with a suspected, but still not definitive etiology, highlights how the current antenatal workup is still limited for several reasons. First of all, the underlying pathogenic mechanism of NIFH remains unclear: it is not known why not all cardiac malformations or not all fetuses affected by the same aneuploidy (i.e. Down syndrome or others) develop hydrops. There are probably yet unknown additional factors, such as epigenetic modifiers that can contribute to fetal hydrops and its severity (14). Although the recent implementation of genetic testing, especially CMA which identify copy number variations, has increased the number of genetic abnormalities detected, single gene disorders due to point mutations or small insertions or deletions are not detected by these tests. In fact, karyotype and CMA will not identify many genetic syndromes that cause NIFH such as the Rasopathies (e.g. Noonan syndrome), inborn errors of metabolism and rare autosomal recessive conditions (10, 14-16). With the introduction of gene panel testing, and most recently the use of prenatal exome sequencing, an increase in the diagnostic rate is expected. In the future the routine use of next-generation sequencing (NGS) specifically focussing on a panel of genes that are known to contribute to the development of NIFH, will further improve the diagnostic rate (17). This is particularly relevant when counselling the parents, not only for the prognosis of an ongoing pregnancy but also for the assessment of recurrence risk in subsequent pregnancies. Therefore, cases with NIFH should be promptly referred to a tertiary level centre to be offered more extensive genetic testing and the option of fetal therapy when relevant. We are currently undertaking further research at St George's Hospital, supported by the British Heart Foundation, looking to improve our ability to better recognise cases of genetic NIFH and improve our interpretation of the genomic data.

Strengths and limitations of the study

This is one of the few studies focusing on the GA at onset of NIFH as an important determinant of the etiology and perinatal outcome. As this is a retrospective study, the risk of bias due to case selection is a recognised limitation. Similarly, the high rate of TOP could have introduced a selection

bias, as severe cases are more likely to be terminated. Moreover, cases with a likely better prognosis were offered fetal intervention. On the other hand, including all cases offers a more comprehensive assessment of NIFH and its evolution at different GA, helping the clinicians to provide individualized management and parental counselling. Another limitation is the lack of available data on the long-term neurodevelopmental outcome of survivors.

Conclusions

The prognosis in NIFH is likely to be related to the underlying etiology. However, the etiology remains unknown in a significant proportion of the cases. Earlier GA at diagnosis was associated with the risk of aneuploidy and worse pregnancy outcomes, including higher risk of perinatal loss. Prenatal intervention is associated with better survival. Large prospective multicentre studies with planned long-term follow-up are needed in order to provide individualised management and parental counselling enabling them to make an informed choice.

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Figure legends

Figure 1. Distribution of chromosomal abnormalities in non-immune hydrops fetalis diagnosed in the first trimester

Figure 2. Distribution of etiological infective agents in pregnancies complicates by non-immune fetal hydrops (across all groups)

Table 1. General characteristics of the study population

	Study cohort (n=279)
Maternal age in years, median (range)	31 (19-44)
Body mass index in Kg/m2, median (range)	24.8 (16.6-49.8)
Nulliparous (n, %)	122 (43.7)
Gestational age at diagnosis in weeks, median (range)	20 (9-37)
Ethnicity (n, %)	
Caucasian	203 (72.8)
Black - African	17 (6.1)
Black - Caribbean	4 (1.4)
South Asian	17 (6.1)
East Asian	5 (1.8)
Asian	11 (4.0)
Other	22 (7.9)

Table 2. Aetiological classification of non-immune fetal hydrops in singleton pregnancies according to the gestational age at initial diagnosis

	Group A (n=63)	**Group B (n=106)**	**Group C (n=74)**	**p-value**
Chromosomal abnormality	44 (69.8)	22 (20.9)	3 (4.1)	<0.001
Single-gene disorders	2 (3.2)	8 (7.5)	6 (8.1)	0.44
Cardiovascular abnormality (structural/rhythm)	7 (11.1)	9 (8.5)	17 (23)	0.02
Other structural abnormalities	2 (3.2)	8 (7.5)	8 (10.8)	0.23
Congenital infection	0 (0)	21 (19.9)	5 (6.7)	<0.001
Hematologic etiology	0 (0)	3 (2.8)	7 (9.5)	0.01
Placental Chorioangioma	0 (0)	1 (0.9)	5 (6.7)	0.02
Feto-maternal haemorrhage	0 (0)	1 (0.9)	0 (0)	0.52
Unknown etiology	6 (9.5)	33 (31.1)	23 (31.1)	0.003

The values represent the numbers (%).

Table 3. Pregnancy outcomes of non-immune hydrops fetalis according to gestational age at the initial diagnosis

Pregnancy outcome	Group A (n=15)	Group B (n=64)	Group C (n=73)	P value
Livebirth, n (%)	3 (20)	26 (40.6)	45 (61.7)	0.003
Neonatal death, n (%)	2 (13.3)	6 (9.4)	16 (21.9)	0.12
Intrauterine demise or miscarriage, n (%)	10 (66.7)	32 (50)	12 (16.4)	<0.001

Pregnancies undergoing termination were not included in this analysis.

Table 4. Distribution of etiologies according to fetal intervention

	Fetal therapy (N=48)	**No Fetal Therapy (N=104)**	**p-value**
Chromosomal	2 (4.2)	14 (13.5)	0.08
Cardiac	2 (4.2)	12 (11.5)	0.14
Genetic	1 (2.1)	10 (9.6)	0.10
Structural Abnormality	2(4.2)	7 (6.7)	0.53
Infection	*12 (25)*	*9 (8.7)*	*0.007*
Anemia	*6 (12.5)*	*3 (2.9)*	*0.02*
Unknown	19 (39.5)	35 (33.6)	0.48
Arrhythmia	1 (2.1)	11 (10.6)	0.07
Placental Chorioangioma	3 (6.2)	3 (2.9)	0.32

Figure 1. Distribution of chromosomal abnormalities in non-immune hydrops fetalis diagnosed in the first trimester

Other included a case of unbalanced translocation

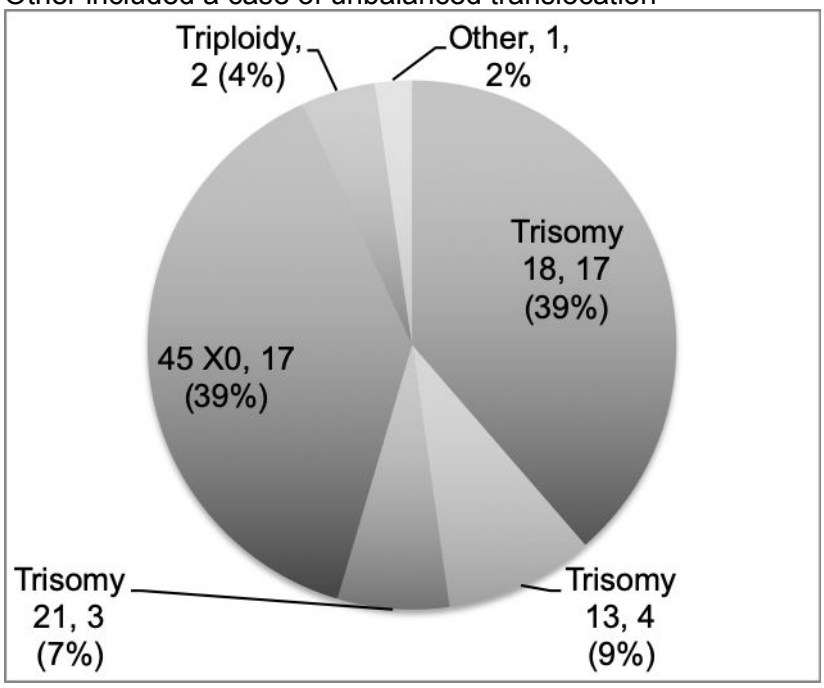

Figure 2. Distribution of etiological infective agents in pregnancies complicates by non-immune fetal hydrops (across all groups)