Ultrasound Obstet Gynecol 2020; **56**: 416–421
Published online 7 August 2020 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.22019.

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

F. G. SILEO[1], A. KULKARNI[2], I. BRANESCU[2], T. HOMFRAY[3], E. DEMPSEY[3], S. MANSOUR[3,4], B. THILAGANATHAN[1,4], A. BHIDE[1] and A. KHALIL[1,4]

[1]*Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, UK;* [2]*Neonatal Unit, St George's Hospital, St George's University of London, London, UK;* [3]*SW Thames Regional Genetics Service, St George's Hospital, St George's University of London, London, UK;* [4]*Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK*

KEYWORDS: etiology; gestational age; hydrops; karyotype; mortality; outcome; trimester

CONTRIBUTION

What are the novel findings of this work?
Non-immune fetal hydrops (NIFH) has significantly different etiology according to the gestational age at its diagnosis. NIFH diagnosed in the first trimester is associated with an increased risk of aneuploidy and a higher risk of perinatal loss. The etiology remains unknown in at least one-third of NIFH cases diagnosed in the second and third trimesters.

What are the clinical implications of this work?
NIFH is a severe condition with a guarded prognosis. Gestational age at diagnosis is a crucial aspect of counseling. Pregnancy outcome differs significantly across the three trimesters, with higher live-birth rates when NIFH is diagnosed later in pregnancy. Fetal therapy, although not resolving the condition itself, is associated with improved survival.

ABSTRACT

Objective *Fetal hydrops is associated with increased perinatal morbidity and mortality. The etiology and outcome of fetal hydrops may differ according to the gestational age at diagnosis. The aim of this study was to evaluate the cause, evolution and outcome of non-immune fetal hydrops (NIFH), according to the gestational age 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, UK, between 2000 and 2018. All fetuses had detailed anomaly and cardiac ultrasound scans, karyotyping and infection screening. Prenatal diagnostic and therapeutic intervention, gestational age at diagnosis and delivery, as well as pregnancy outcome, 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. The etiology of the condition varied significantly in the three trimesters. Excluding 30 women who declined invasive testing, the cause of NIFH was defined as unknown in 62 of the remaining 243 cases (25.5%). Chromosomal aneuploidy was the most common cause of NIFH in the first trimester. It continued to be a significant etiologic factor in the second trimester, along with congenital infection. In the third trimester, the most common etiology was cardiovascular abnormality. Among the 152 (55.7%) women continuing the pregnancy, 48 (31.6%) underwent fetal intervention, including the insertion of pleuroamniotic shunts, fetal blood transfusion and thoracentesis. Fetal intervention was associated significantly with lower perinatal mortality (odds ratio (OR), 0.30 (95% CI, 0.14–0.61);* $P < 0.001$*); this association remained significant after excluding cases with a diagnosis of anemia or infection (OR, 0.29 (95% CI, 0.13–0.66);* $P = 0.003$*). In 104 fetuses not undergoing active fetal intervention, the gestational age at diagnosis was the only parameter that was significantly associated with the risk of perinatal mortality (OR, 0.92 (95% CI, 0.85–0.99);* $P = 0.035$*), while the affected body cavity and polyhydramnios were not (*$P > 0.05$*).*

Correspondence to: Prof. A. Khalil, Fetal Medicine Unit, St George's University of London, London SW17 0RE, UK (e-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com)

Accepted: 7 March 2020

Conclusions *An earlier gestational age at diagnosis of NIFH was associated with an increased risk of aneuploidy and worse pregnancy outcome, including a higher risk of perinatal loss. Fetal therapy was associated significantly with lower perinatal mortality. © 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Despite advances in fetal medicine, the perinatal mortality associated with fetal hydrops remains high. Fetal hydrops is a pathologic condition characterized by deranged fluid homeostasis, leading to abnormal fluid accumulation in the fetal interstitial spaces[1,2]. It is detected traditionally by ultrasound examination and defined as the presence of fluid in two or more fetal serous cavities, including skin edema, ascites, and pleural and/or pericardial effusion[3]. Historically, most cases of fetal hydrops were attributable to red-cell alloimmunization and defined as immune hydrops fetalis. Thanks to the introduction and widespread use of rhesus (D) immunoglobulin, non-immune fetal hydrops (NIFH) accounts now for almost 90% of hydrops cases, 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 the 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.*[9], were aneuploidy (19%), cardiovascular abnormality (15%), infection (14%) and thoracic disorders (12%). Other conditions associated with NIFH include syndromic, single-gene and metabolic disorders, twin–twin transfusion syndrome (TTTS), congenital infection, placental abnormality and fetal tumors[3].

Previous studies do not enable us to provide individualized assessment and counseling, 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 etiology, evolution and outcome of NIFH, according to GA at diagnosis, and to determine the factors which influence the perinatal outcome in these pregnancies.

PATIENTS AND METHODS

This was a retrospective study of all NIFH cases referred to our Fetal Medicine Unit at St George's University Hospital, London, UK, between 2000 and 2018. Our Fetal Medicine Unit is a tertiary referral center 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 edema, in the absence of atypical red-cell antibodies. All fetuses underwent detailed structural and cardiac ultrasound examinations. Ultrasound scans were performed using 3–5-MHz convex sector probes and GE Voluson E8 or E10 (GE Medical Systems, Zipf, Austria), Toshiba Aplio (Toshiba, Tokyo, Japan), Aloka 4000 (Hitachi Aloka Medical, Twinsburg, OH, USA) and Philips iU22 (Philips Medical Systems, Solingen, Germany) ultrasound machines.

All pregnant women were offered fetal karyotyping, maternal infection screening (toxoplasmosis, cytomegalovirus (CMV) and parvovirus B19, among others, depending on the relevant history) and Kleihauer–Betke testing. Rubella immunological serology, treponemal screening and maternal hemoglobin electrophoresis were ascertained from 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 included chromosomal microarray (CMA), which was 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 twin pregnancy due to TTTS and cases for which the pregnancy outcome was not available.

We classified the etiology of NIFH into nine main groups: chromosomal abnormality, single-gene disorder, cardiovascular (structural, functional or rhythm) abnormality, other structural abnormality, congenital infection (such as parvovirus B19, CMV or toxoplasmosis), placental chorioangioma, hematologic etiology, fetomaternal hemorrhage and unknown etiology. Prenatal diagnostic and therapeutic intervention, 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 diagnosis of NIFH: Group A, up to 13 + 6 weeks; Group B, from 14 to 24 + 6 weeks; and Group C, from 25 weeks onward. We chose to divide Groups B and C at 24–25 weeks so the option of TOP was still available as a choice for women up until 24 weeks' gestation.

We also reviewed the detailed neonatal electronic records of pregnancies with an antenatal diagnosis of NIFH, delivered 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 are presented as mean ± SD or median (range). Binary and categorical variables are presented as *n* (%). Distribution assumptions for continuous variables were assessed visually with quantile–quantile plots, and then were confirmed with the Shapiro–Wilk test. Continuous variables were compared using the unpaired Student's *t*-test or Mann–Whitney *U*-test, while the chi-square test was used for binary or categorical variables. A 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. Statistical analyses were performed using IBM SPSS Statistics Version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Study population

NIFH was diagnosed in 279 pregnancies between 2000 and 2018. Table 1 shows the general characteristics of our population, which included fetuses from six (2.2%) dichorionic diamniotic twin pregnancies. Due to their limited number, which prevented meaningful conclusions, twin pregnancies were excluded from further analysis and their data are presented in Table S1. We divided the remaining 273 singleton pregnancies into three different groups according to the GA at onset of NIFH: 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 onwards ($n = 82$).

Etiologic classification of NIFH

The distribution of etiologies varied significantly in all three trimesters. Excluding 30 women who did not undergo invasive testing (11 in the first, 11 in the second and eight in the third trimester), and in whom ultrasound examination failed to reveal an obvious identifiable etiology, the cause of NIFH was unknown in 62 of the 243 cases (25.5%; $P = 0.003$). Table 2 presents the etiologic classification of NIFH in these pregnancies, according to the GA at diagnosis.

In Group A, NIFH was due to chromosomal abnormalities in more than two-thirds (69.8%) of cases; Table 3 shows the distribution of chromosomal abnormalities diagnosed. In Group B, 33/106 (31.1%) cases with NIFH were due to an unknown etiology. Congenital infection was the second most common cause of NIFH in 21/106 (19.8%) fetuses; the most common infection was parvovirus B19, affecting 17 (81.0%) cases, while CMV and toxoplasmosis affected three (14.3%) and one (4.8%) cases, respectively. Table 4 shows the distribution of infective agents in Groups B and C. In Group C, the etiology of NIFH was unknown in 23/74 (31.1%) cases. Cardiovascular abnormality was the second most common cause of NIFH (17/74; 23.0%) with arrhythmia being the etiology in 11/17 (64.7%) cases. The suspected cause of NIFH in cases with an unknown etiology in all three trimesters is presented in Table S2.

Pregnancy outcome in NIFH

TOP was performed in 121/273 (44.3%) of the included cases, comprising 59 (79.7%), 53 (45.3%) and nine (11.0%) cases in Groups A, B and C, respectively. Live-birth and intrauterine-demise (IUD)/miscarriage rates were significantly different according to the GA at the initial diagnosis, as shown in Table 5.

Among the 152 (55.7%) women continuing their pregnancy, 48/152 (31.6%) underwent fetal intervention

Table 1 Maternal characteristics in 273 singleton and six twin pregnancies with non-immune fetal hydrops

Characteristic	*Value*
Maternal age (years)	31 (19–44)
Body mass index (kg/m^2)	24.8 (16.6–49.8)
Nulliparous	122 (43.7)
Gestational age at diagnosis (weeks)	20 (9–37)
Ethnicity	
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 (3.9)
Other	22 (7.9)

Data are given as median (range) or *n* (%).

Table 3 Distribution of chromosomal abnormalities in 44 fetuses with non-immune fetal hydrops diagnosed in first trimester

Chromosomal abnormality	n *(%)*
Triploidy	2 (4.5)
45,X0	17 (38.6)
Trisomy 13	4 (9.1)
Trisomy 18	17 (38.6)
Trisomy 21	3 (6.8)
Other	1 (2.3)

Table 2 Etiology of non-immune fetal hydrops in 243 singleton pregnancies that underwent invasive testing, according to gestational age at initial diagnosis

Etiology	*≤ 13 + 6 weeks* (n = *63*)	*14 to 24 + 6 weeks* (n = *106*)	*≥ 25 weeks* (n = *74*)	P
Chromosomal abnormality	44 (69.8)	22 (20.8)	3 (4.1)	< 0.001
Single-gene disorder	2 (3.2)	8 (7.5)	6 (8.1)	0.44
Cardiovascular abnormality*	8 (12.7)	9 (8.5)	17 (23.0)	0.02
Other structural abnormality	3 (4.8)	8 (7.5)	8 (10.8)	0.41
Congenital infection	0 (0)	21 (19.8)	5 (6.8)	< 0.001
Hematologic etiology	0 (0)	3 (2.8)	7 (9.5)	0.01
Placental chorioangioma	0 (0)	1 (0.9)	5 (6.8)	0.02
Fetomaternal hemorrhage	0 (0)	1 (0.9)	0 (0)	0.52
Unknown etiology	6 (9.5)	33 (31.1)	23 (31.1)	0.003

Data are given as *n* (%). *Structure/rhythm.

Table 4 Distribution of etiologic infective agents in pregnancies complicated by non-immune fetal hydrops in 26 fetuses in second and third trimesters

Infective agent	n *(%)*
Syphilis	1 (3.8)
Varicella	1 (3.8)
Cytomegalovirus	4 (15.4)
Toxoplasma	2 (7.7)
Parvovirus B19	18 (69.2)

Table 5 Outcome of 152 pregnancies with non-immune fetal hydrops*, according to gestational age at initial diagnosis

Outcome	*≤ 13 + 6 weeks* (n = *15*)	*14 to 24 + 6 weeks* (n = *64*)	*≥ 25 weeks* (n = *73*)	P
Live birth	3 (20)	26 (40.6)	45 (61.6)	0.003
Neonatal death	2 (13.3)	6 (9.4)	16 (21.9)	0.12
IUD or miscarriage	10 (66.7)	32 (50)	12 (16.4)	< 0.001

Data are given as *n* (%). *Patients who opted for termination of pregnancy were not included in analysis (*n* = 121). IUD, intrauterine demise.

Table 6 Etiology of non-immune fetal hydrops in 152 pregnancies*, according to whether they underwent fetal intervention

Etiology	*Fetal therapy* (n = *48*)	*No fetal therapy* (n = *104*)	P
Chromosomal abnormality	2 (4.2)	14 (13.5)	0.08
Cardiac abnormality	2 (4.2)	12 (11.5)	0.14
Single-gene disorder	1 (2.1)	10 (9.6)	0.10
Structural abnormality	2 (4.2)	7 (6.7)	0.53
Infection	12 (25.0)	9 (8.7)	0.007
Anemia	6 (12.5)	3 (2.9)	0.02
Arrhythmia	1 (2.1)	11 (10.6)	0.07
Placental chorioangioma	3 (6.3)	3 (2.9)	0.32
Unknown	19 (39.6)	35 (33.7)	0.48

Data are given as *n* (%). *Patients who opted for termination of pregnancy were not included in analysis (*n* = 121).

(pleuroamniotic shunt (uni or bilateral), intrauterine transfusion, thoracentesis or paracentesis, intrauterine administration of digoxin through cordocentesis, interstitial laser for chorioangioma). Data regarding the type of fetal intervention, etiology of NIFH and GA at diagnosis are presented in Table S3. Congenital infection and fetal anemia were significantly more frequent in fetuses that underwent intervention compared to those who did not (25.0% *vs* 8.7% ($P = 0.007$) and 12.5% *vs* 2.9% ($P = 0.02$), respectively), while the other etiologies did not differ significantly between the two groups (Table 6). The mean GA at diagnosis and at birth differed significantly between the group who underwent fetal intervention compared to the group who did not (27.1 *vs* 23.4 ($P < 0.001$) and 32.8 *vs* 29.4 ($P = 0.008$), respectively), while there was no significant difference in the rate of resolved hydrops between pregnancies that underwent fetal intervention (29.2%) and those which did not (19.2%); odds ratio (OR), 1.73 (95% CI, 0.78–3.81); $P = 0.17$). However, we observed a significantly lower risk of perinatal death in pregnancies that 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 infection and anemia as treatable causes of NIFH, and likely to be associated with better outcome, we performed the same analysis after excluding cases with infection or anemia from the two groups. After excluding 12 cases of infection and six cases of anemia from the fetal therapy group, and nine and three cases of infection and anemia, respectively, from the group that did not undergo fetal therapy, we still observed a significantly lower risk of perinatal death in 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, the presence of concomitant polyhydramnios and the risk of perinatal mortality, was performed in 104 fetuses with NIFH that did not receive fetal therapy. The GA at diagnosis was the only variable that was associated, inversely, with the risk of perinatal mortality (OR 0.92, (95% CI, 0.85–0.99); $P = 0.035$). No significant association was observed with pleural effusion (OR 0.88, (95% CI, 0.35–2.19); $P = 0.780$), pericardial effusion (OR, 2.32 (95% CI, 0.87–6.19); $P = 0.090$), ascites (OR, 1.06 (95% CI, 0.39–2.93); $P = 0.910$), skin edema (OR, 1.04 (95% CI, 0.41–2.62); $P = 0.940$), cystic hygroma (OR, 0.66 (95% CI, 0.11–4.07); $P = 0.660$) or polyhydramnios (OR, 1.74 (95% CI, 0.54–5.6); $P = 0.230$).

DISCUSSION

Summary of study findings

The etiology of NIFH varied significantly between the three trimesters of pregnancy. Chromosomal abnormality represented the most common etiology of NIFH in the first trimester, while the etiology remained unknown in at least one-third of the cases later in pregnancy. Fetal intervention was associated significantly with lower perinatal mortality. In fetuses that did not undergo active fetal intervention, GA at diagnosis was the only parameter that was associated significantly with the risk of perinatal mortality.

Interpretation of findings and comparison with published literature

Excluding 30/273 (11.0%) fetuses for which karyotype was not available, as the parents declined investigation and therefore aneuploidy or genetic cause could not

be ruled out, the etiology of fetal hydrops could be identified in 74.5% (181/243) of our study population. The proportion of cases receiving a definitive diagnosis was slightly lower than that reported in published reviews of the literature[8,10], and therefore, we reviewed cases with an unknown etiology to look for a possible explanation. Among 62/243 cases with an unknown diagnosis, an abnormal posture of the fetus was observed in 6/243 (2.5%) cases, suggesting a neuromuscular disorder, while in 8/243 (3.3%) cases, a genetic cause was suspected, but not identified, leaving true idiopathic etiology in 19.8% (48/243) of the study cohort, which is consistent with the published literature (Table S2)[8].

Clinical and research implications

An important aspect in counseling prospective parents should be the GA at diagnosis of NIFH. As shown in this study, pregnancy outcome differs significantly, with higher live-birth rates when NIFH was diagnosed later in pregnancy. GA at diagnosis is likely to be related to the cause, with aneuploidy being the most common cause in the first trimester, and thus influencing the prognosis. It is not surprising that almost 80% of women opted for 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 a guarded prognosis. Even when excluding chromosomal abnormality as a possible confounding factor influencing prognosis, live-birth and IUD/miscarriage rates were significantly different according to the GA at initial diagnosis (Table S4). Survival was also influenced by fetal intervention. Although it did not necessarily resolve the hydrops itself, it was associated with improved survival; this was also confirmed after excluding fetuses with NIFH due to anemia or infection, for which a treatable and/or resolving cause is likely to be associated with a better prognosis, increasing the strength of this observation.

The high proportion of cases with a suspected, but 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 unknown why not all cardiac malformations or not all fetuses affected by the same aneuploidy (such as Down syndrome or others) develop hydrops. It is also likely that unknown additional factors, such as epigenetic modifiers, can contribute to fetal hydrops and its severity[14]. Although the recent implementation of genetic testing, especially CMA, which identifies 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 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, routine use of next-generation sequencing, specifically focusing on a panel of genes that are known to contribute to the development of NIFH, will improve further the diagnostic rate[17]. This is particularly relevant when counseling parents, not only for the prognosis of an ongoing pregnancy, but also for the assessment of a recurring risk in subsequent pregnancies. Therefore, cases with NIFH should be referred promptly to a tertiary level center to be offered more extensive genetic testing and the option of fetal therapy where relevant. We are currently undertaking further research at St George's Hospital, supported by the British Heart Foundation, to improve our ability to recognize better cases of genetic NIFH and improve our interpretation of the genomic data.

Strengths and limitations

This is one of the few studies focusing on GA at the 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 recognized 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 GAs, helping clinicians to provide individualized management and parental counseling. 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, etiology remains unknown in a significant proportion of cases. An earlier GA at diagnosis was associated with the risk of aneuploidy and worse pregnancy outcome, including a higher risk of perinatal loss. Prenatal intervention is associated with better survival. Large prospective multicenter studies with planned long-term follow-up are needed in order to provide individualized management and counseling, enabling parents to make an informed choice.

REFERENCES

1. Castillo RA, Devoe LD, Hadi HA, Martin S, Geist D. Nonimmune hydrops fetalis: clinical experience and factors related to a poor outcome. *Am J Obstet Gynecol* 1986; **155**: 812-816.
2. Norton ME. Nonimmune hydrops fetalis. *Semin Perinatol* 1994; **18**: 321–332.
3. Norton ME. Chauhan SP. Dashe JS. Society for Maternal–Fetal Medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. *Am J Obstet Gynecol* 2015; **212**: 127–139.
4. Santolaya J, Alley D, Jaffe R, Warsof SL. Antenatal classification of hydrops fetalis. *Obstet Gynecol* 1992; **79**: 256–259.
5. Heinonen S, Ryynänen M, Kirkinen P. Etiology and outcome of second trimester non-immunologic fetal hydrops. *Acta Obstet Gynecol Scand* 2000; **79**: 15–18.
6. Machin GA. Hydrops revisited: literature review of 1,414 cases published in the 1980s. *Am J Med Genet* 1989; **34**: 366–390.
7. Hutchison AA, Drew JH, Yu VY, Williams ML, Fortune DW, Beischer NA. Nonimmunologic hydrops fetalis: a review of 61 cases. *Obstet Gynecol* 1982; **59**: 347–352.

8. Bellini C, Hennekam RC. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. *Am J Med Genet A* 2012; **158A**: 597–605.
9. Santo S, Mansour S, Thilaganathan B, Homfray T, Papageorghiou A, Calvert S, Bhide A. Prenatal diagnosis of non-immune hydrops fetalis: what do we tell the parents? *Prenat Diagn* 2011; **31**: 186–195.
10. Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA, Hennekam RC. Etiology of non-immune hydrops fetalis: An update. *Am J Med Genet Part A* 2015; **167A**: 1082–1088.
11. Abrams ME, Meredith KS, Kinnard P, Clark RH. Hydrops fetalis: a retrospective review of cases reported to a large national database and identification of risk factors associated with death. *Pediatrics* 2007; **120**: 84–89.
12. Lallemand AV, Doco-Fenzy M, Gaillard DA. Investigation of nonimmune hydrops fetalis: multidisciplinary studies are necessary for diagnosis e review of 94 cases. *Pediatr Dev Pathol* 1999; **2**: 432–439.
13. Jauniaux E, Van Maldergem L, De Munter C, Moscoso G, Gillerot Y. Nonimmune hydrops fetalis associated with genetic abnormalities. *Obstet Gynecol* 1990; **75**: 568–572.
14. Sparks TN, Thao K, Lianoglou BR, Boe NM, Bruce KG, Datkhaeva I, Field NT, Fratto VM, Jolley J,Laurent LC, Mardy AH, Murphy AM, Ngan E, Rangwala N, Rottkamp CAM, Wilson L, Wu E, Uy CC, Valdez Lopez P, Norton ME; University of California Fetal–Maternal Consortium (UCfC). Nonimmune hydrops fetalis: identifying the underlying genetic etiology. *Genet Med* 2019; **21**: 1339–1344.
15. Hellmund A, Berg C, Geipel A, Müller A, Gembruch U. Prenatal diagnosis of fetal akinesia deformation sequence (FADS): a study of 79 consecutive cases. *Arch Gynecol Obstet* 2016; **294**: 697–707.
16. Gimovsky AC, Luzi P, Berghella V. Lysosomal storage disease as an etiology of nonimmune hydrops. *Am J Obstet Gynecol* 2015; **212**: 281–290.
17. Sudrié-Arnaud B, Marguet F, Patrier S, Martinovic J, Louillet F, Broux F, Charbonnier F, Dranguet H, Coutant S, Vezain M, Lanos R, Tebani A, Fuller M, Lamari F, Chambon P, Brehin AC, Trestard L, Tournier I, Marret S, Verspyck E, Laquerrière A, Bekri S. Metabolic causes of nonimmune hydrops fetalis: A next-generation sequencing panel as a first-line investigation. *Clin Chim Acta* 2018; **481**: 1–8.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Data regarding six dichorionic diamniotic twin pregnancies

Table S2 Evaluation of non-immune fetal hydrops with an unknown etiology in all three trimesters of pregnancy

Table S3 Data regarding type of fetal intervention, etiology of non-immune fetal hydrops and gestational age (GA) at diagnosis in 48 pregnancies that underwent fetal intervention

Table S4 Pregnancy outcome in 136 cases of non-immune fetal hydrops, according to gestational age at initial diagnosis after excluding all cases of termination of pregnancy and chromosomal abnormalities