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Society for Maternal-Fetal Medicine Consult Series #75: Evaluation and management of non-immune hydrops fetalis

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Replaces SMFM Clinical Guideline #7: Non-immune hydrops fetalis

Abstract

Non-immune hydrops fetalis (NIHF) can result from a multitude of underlying causes, such as fetal genetic diseases, congenital anomalies, infections, fetal arrhythmias, placental tumors, monochorionic twin complications, and other disorders. Management is complex and rooted in the preferences of the pregnant individual and the known or suspected etiology of NIHF. In this Consult, we review general considerations and a contemporary approach to the diagnosis, evaluation, and management of NIHF, providing recommendations based on the available evidence. The following are the Society for Maternal-Fetal Medicine's recommendations: (1) we recommend fetal diagnostic testing for all pregnancies when one or more fetal effusions are detected; this testing should include chromosomal microarray analysis (CMA) with or without karyotype. When infectious etiologies are in the differential diagnosis, polymerase chain reaction studies should also be performed (grading of recommendations assessment, development, and evaluation [GRADE] 1C); (2) we recommend that exome or genome sequencing be offered in pregnancies with NIHF or NIHF spectrum following CMA or karyotype that does not yield a diagnosis and in the absence of another suspected etiology. If the risk of aneuploidy is low or a single-gene disorder is strongly suspected, offering exome or genome sequencing concurrently with CMA is reasonable (GRADE 1C); (3) we recommend that all patients who develop mirror syndrome in the setting of NIHF receive individualized counseling about delivery or abortion care; expectant management should be reserved only for rare circumstances, after counseling about the maternal risks and shared decision-making (GRADE 1C); (4) given the associated maternal risks, we recommend that all patients with pregnancies complicated by NIHF receive individualized counseling and be offered all management options, including abortion care (GRADE 1C); (5) we recommend that timing of delivery be individualized for each pregnancy with NIHF and that preterm delivery be reserved for obstetrical indications such as preeclampsia or mirror syndrome, preterm labor or premature rupture of membranes, new or worsening NIHF, or

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when the overall maternal or fetal risks of continued management are expected to outweigh those of delivery (GRADE 1C); (6) we recommend antenatal corticosteroids for continuing pregnancies with NIHF when preterm delivery is anticipated within 7 days, if neonatal resuscitation is desired and would be offered (GRADE 1C); (7) we recommend that cesarean delivery be performed for standard obstetrical indications in the setting of NIHF when postnatal resuscitation and life-supporting care are planned for the neonate (GRADE 1C). This Consult replaces Society for Maternal-Fetal Medicine Clinical Guideline #7: Non-immune hydrops fetalis.

KEYWORDS

congenital anomaly, congenital infection, fetal effusion, genetic disease, hydrops fetalis, mirror syndrome, non-immune hydrops fetalis, non-immune hydrops fetalis spectrum, preterm birth, ultrasound

1 | INTRODUCTION

Hydrops fetalis is a Greek term that describes pathological fluid (ὕδωρ, Greek for water) accumulation in fetal soft tissues and serous cavities. Hydrops has been defined as the presence of abnormal fluid collections in two or more fetal compartments. These include ascites, pleural effusions, pericardial effusion (defined as >2–3 mm), and generalized skin edema (defined as skin thickness >5 mm) (Figure 1) [1, 2]. These features can be detected by routine obstetric ultrasonography. Other frequent sonographic findings, though not formal components of the diagnostic criteria, include placentomegaly (defined as placental thickness ≥4 cm in the second trimester or ≥6 cm in the third trimester) and polyhydramnios (defined as either deepest vertical pocket ≥8 cm or amniotic fluid index of ≥24 cm) [3–6].

Non-immune hydrops fetalis (NIHF) refers specifically to hydrops not caused by red cell alloimmunization. With the widespread use of Rh(D) immune globulin, the prevalence of Rh(D) alloimmunization and associated hydrops has dramatically decreased. As a result, NIHF accounts for almost 90% of hydrops fetalis cases [7], with a reported prevalence of one in 1700–3000 pregnancies or one in 4000 live births [8–11]. However, many published series predate contemporary sonography, and limited information is available on the current prevalence of NIHF or how this prevalence varies across populations.

NIHF is heterogeneous and can result from a multitude of underlying causes, including fetal genetic diseases, congenital anomalies, congenital infections, fetal arrhythmias, placental tumors (e.g., chorioangiomas), monochorionic twin complications (e.g., twin-twin transfusion syndrome [TTTS]), and other disorders. This Consult focuses mainly on NIHF in the absence of monochorionic twin complications.

Many series have demonstrated significant overlap in the non-immune etiologies that underlie single and multiple effusions, indicating that there is a spectrum of diagnoses capable of presenting with fetal effusions [12–20]. Examples are Noonan syndrome presenting with either pleural effusions or generalized NIHF, inborn errors of metabolism presenting with either ascites or NIHF, and parvovirus presenting with pleural or pericardial effusions or with NIHF. The diagnostic evaluations performed in pregnancies with single and multiple fetal effusions or NIHF are largely the same, and pregnancies with a single fetal effusion should be monitored for progression to NIHF. From a diagnostic perspective, one fetal effusion (pleural effusion, pericardial effusion, ascites, or skin edema) may be referred to as "hydrops fetalis spectrum," and one fetal effusion resulting from non-immune etiologies as "NIHF spectrum." Exceptions are pregnancies with fetal fluid collections resulting from a specific process (e.g., ascites from a ruptured urinoma or fetal bladder or skin edema from amniotic band syndrome [21–23]) rather than from a systemic process (e.g., a viral infection or genetic disorder). Importantly, while similar underlying diagnoses should be considered for fetuses with single or multiple effusions, outcomes for the fetus and neonate vary widely and depend on the underlying etiology, number and severity of fetal effusions, gestational age at birth, and other factors. Thus, the management, prognosis, and ultimate outcomes are not necessarily equivalent between fetuses with only one effusion as compared to those with NIHF, and the discussion in this document regarding clinical management is based on existing literature for NIHF with two or more fetal effusions.

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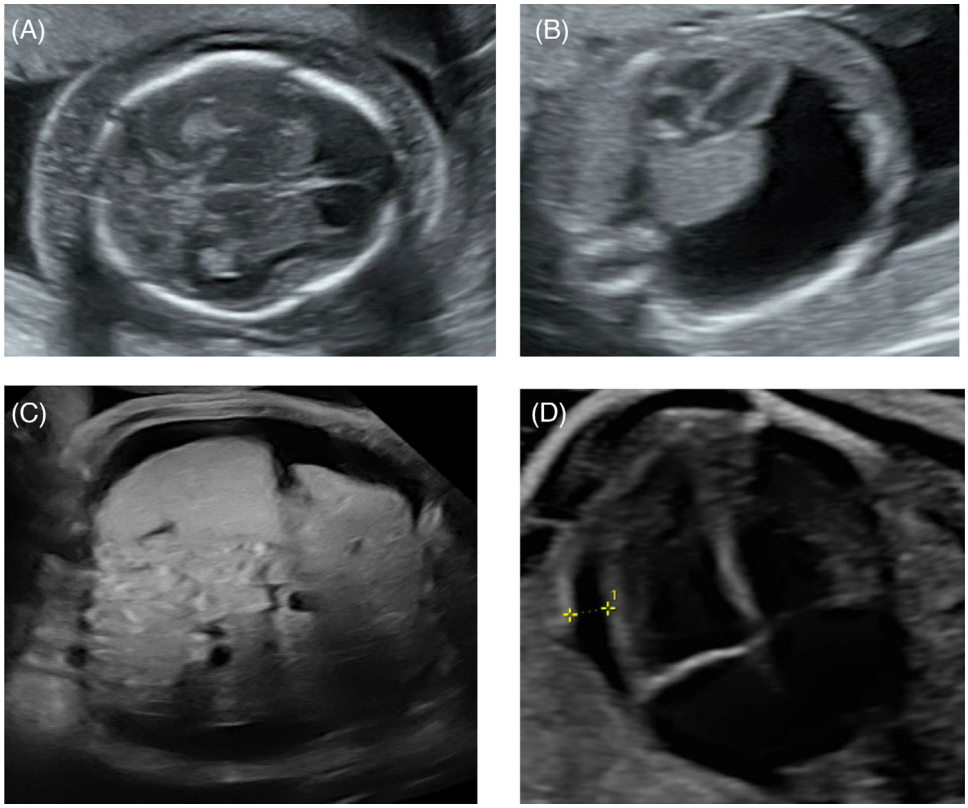


FIGURE 1 Sonographic features that may be seen with non-immune hydrops fetalis or non-immune hydrops fetalis spectrum. (A) Skin edema surrounding the fetal cranium. (B) Large unilateral pleural effusion. (C) Ascites, transverse, at the level of the fetal liver and bowel. (D) Pericardial effusion, four-chamber view.

2 | CLINICAL QUESTIONS

2.1 | What is the underlying pathogenesis of NIHF?

A common pathophysiology underlying many etiologies of NIHF spectrum disorder is an imbalance in the regulation of fluid movement between the vascular and interstitial spaces, with an increase in interstitial fluid production or lymphatic vessel dysplasia with a decrease in lymphatic return [24]. Other mechanisms include right heart failure and volume overload leading to increased central venous pressure and secondary hepatic dysfunction (e.g., structural heart defects); obstruction of venous or arterial blood flow (e.g., pulmonary masses); inadequate diastolic ventricular filling (e.g., arrhythmias); liver failure or hepatic venous congestion leading to decreased hepatic function and hypoalbuminemia (e.g., inborn errors of metabolism); increased capillary permeability (e.g., infections); fetal anemia leading to high-output cardiac failure and extramedullary hematopoiesis, often with resultant hepatic dysfunction (e.g., hereditary anemias); and reduced osmotic pressure (e.g., congenital nephrosis) [25]. The precise pathogenesis depends on the underlying disorder, but the pathophysiology is not well understood for all causes of fetal effusions.

2.2 | What are the causes of NIHF?

NIHF and NIHF spectrum can result from a large number of underlying fetal and placental abnormalities (Table 1) as well as genetic disorders (Table 2). The differential diagnosis is extensive, and historically, the underlying cause has remained uncertain in many pregnancies due to a lack of comprehensive testing options [26, 27]. Recent advances in genetic testing have greatly improved the ability to diagnose the many underlying genetic disorders associated with one or more fetal effusions [16, 25, 28–33]. A thorough evaluation and accurate diagnosis are critical for determining prognosis and recurrence risk.

Disease processes that can lead to fetal effusions are presented in this section by topic: genetic disorders, structural or functional abnormalities of the fetus, fetal anemias, structural abnormalities of the placenta and umbilical cord, and infections. However, there can be considerable

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TABLE 1 Approximate frequency of structural fetal anomalies, placental abnormalities, genetic syndromes, and infections among pregnancies with non-immune hydrops fetalis [24, 27, 30].

Etiology of non-immune hydrops fetalis	Proportion[a]
Multiple anomalies/syndromic/genetic[b]	19%–53%
Cardiovascular anomalies	8%–20%
Lymphatic dysplasia	6%–10%
Infection	7%–8%
Pulmonary/thoracic anomalies	5%–6%
Twin-twin transfusion syndrome	4%–5%
Placental chorioangioma	2%
Hematological condition	0%–10%
Genitourinary anomalies	0%–2%
Gastrointestinal condition	0%–1%
Extra-thoracic tumor	0%–1%

[a]These estimates are largely from studies published prior to more widespread use of next-generation sequencing, which can identify single-gene disorders that explain both the fetal anomalies and non-immune hydrops fetalis observed. There may be overlap between categories, such as for fetuses with a cardiac anomaly and a genetic diagnosis. This list is not meant to be all-inclusive; rather, it provides estimates for underlying abnormalities where data are available.

[b]Includes pregnancies with multiple fetal anomalies and genetic disorders.

TABLE 2 Approximate frequencies of genetic disorders underlying pregnancies with non-immune hydrops fetalis spectrum [16, 24, 26, 27, 29, 40, 41].

Fetal genetic disorder	Proportion[a]
Aneuploidy	13%–30%
RASopathies	7%–8%
Inborn errors of metabolism	1%–5%
Other congenital lymphatic anomalies	2%–4%
Akinesia/neurologic disorders	2%
Musculoskeletal disorders	1%–3%
Hereditary anemias	1%–2%
Cardiovascular disorders	1%
Mitochondrial disorders	<1%
Immunologic disorders	<1%
Ciliopathies	<1%
Other	2%–4%

[a]Many of these estimates are extrapolated from studies that used next-generation sequencing for pregnancies with non-immune hydrops fetalis after initial karyotype, chromosomal microarray analysis, and/or additional testing did not yield an explanation.

overlap between causes. For example, even when fetal anomalies are identified in conjunction with one or more fetal effusions, further testing is generally recommended to determine whether a genetic disorder or infectious etiology explains the constellation of findings. It is also important to distinguish fetal effusions that result from a systemic process (e.g., a viral infection or genetic disorder) from fluid collections resulting from a specific issue such as a urinoma or ruptured fetal bladder [21, 22], as the differential diagnosis is quite different in each of these scenarios.

2.2.1 | Genetic disorders

Chromosomal abnormalities, particularly monosomy X (45,X) and trisomy 21, are common causes of NIHF, accounting for 13%–30% of all presentations during pregnancy [24, 26, 34]. Several other chromosomal abnormalities are also associated with NIHF, including trisomy 13, trisomy 18, and triploidy [26, 35, 36]. In pregnancies with trisomy 21 or monosomy X, fetal effusions are thought to result from aberrant communications between the lymphatic and venous systems. Transient abnormal myelopoiesis, a leukemic condition that can manifest with fetal anemia and effusions, occurs in about 10% of infants with trisomy 21 [37–39].

A large number of single-gene disorders have also been recognized as etiologies of NIHF and NIHF spectrum. Such disorders are generally not identified by chromosomal microarray analysis (CMA) or karyotype; rather, detection usually requires either a gene panel or exome or genome sequencing. In this Consult, we discuss some of the more common categories of single-gene disorders underlying NIHF and NIHF spectrum, but many other single-gene disorders can lead to fetal effusions. The RASopathies are a group of single-gene disorders that are estimated to underlie approximately one third of euploid pregnancies with NIHF [16, 40]. The RASopathies are caused by pathogenic variants in genes that are part of the RAS/mitogen-activated protein kinase cascade, which is involved in regulating cell proliferation, differentiation, and survival [41]. The RASopathy spectrum includes Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, and other disorders that can also manifest in utero with cardiac anomalies, fetal arrhythmias, renal anomalies, polyhydramnios, and other features [15, 17]. These disorders are known to present with cystic hygroma or a spectrum of fetal effusions, such as pleural effusions, skin edema, or generalized NIHF [12, 15–17, 40]. As with most single-gene disorders, RASopathies are typically diagnosed by targeted gene panels or by exome or genome sequencing.

Inborn errors of metabolism are estimated to underlie about 1%–5% of pregnancies with NIHF and can manifest with single effusions (most commonly ascites) or generalized NIHF [13, 18, 24, 29]. Additional features can include hepatomegaly, splenomegaly, cardiomyopathy, bony abnormalities such as stippling of the epiphyses, and fetal growth restriction [13, 18]. Examples of commonly

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reported inborn errors of metabolism that present with fetal effusions are mucopolysaccharidosis type VII, infantile sialic acid storage disease, and galactosialidosis [13, 18, 42]. Proposed mechanisms leading to fetal effusions with inborn errors of metabolism include visceromegaly and obstruction of venous return, decreased erythropoiesis and anemia, and hypoproteinemia. Following delivery or termination of pregnancy, histology of the placenta, liver, spleen, heart, blood, bone marrow, and bony morphology can provide additional clues supporting an inborn error of metabolism [18]. However, a definitive molecular diagnosis typically requires DNA testing with a gene panel or exome or genome sequencing.

Congenital lymphatic anomalies other than RASopathies are estimated to underlie approximately 2%–4% of pregnancies with fetal effusions [24, 29]. The RASopathies already discussed can present with lymphedema and chylous effusions, and other disorders of abnormal lymphatic development, such as lymphedema-distichiasis syndrome, Milroy disease, and generalized lymphatic dysplasia, can also present in utero [16, 43]. These disorders can manifest with one or more fetal effusions or with increased nuchal translucency or cystic hygroma early in gestation [16, 43].

Fetal akinesia syndromes can also manifest with one or more fetal effusions, along with craniofacial anomalies, fetal growth restriction, contractures, polyhydramnios, and other features that vary by the specific underlying genetic syndrome [16, 44, 45]. Other single-gene disorders that have been reported with fetal effusions include hereditary anemias, immunologic disorders, mitochondrial disorders, and ciliopathies [16, 24, 27, 29]. While there are some exceptions, such as microdeletions leading to alpha thalassemia, many of these disorders are not identified by CMA and are instead diagnosed through targeted gene panels or with exome or genome sequencing [16, 46, 47].

2.2.2 | Structural or functional abnormalities in the fetus

Cardiovascular abnormalities are the most common structural anomalies associated with fetal effusions and are identified in as many as 20% of all pregnancies with NIHF [24, 30]. Single fetal effusions or NIHF can also result from arrhythmias, cardiomyopathy, or large cardiac tumors [48, 49]. The most common congenital heart defects reported in association with fetal effusions are right heart defects, cardiomyopathy, and hypoplastic left heart syndrome [24, 25, 28, 30]. Certain cardiac abnormalities seen with fetal effusions may increase the risk of a unifying underlying diagnosis and also modify the prognosis, such as pulmonary stenosis in association with Noonan syndrome, cardiac rhabdomyomas with tuberous sclerosis, and myocarditis with infections such as parvovirus [41, 48, 50].

Both tachyarrhythmias and bradyarrhythmias can lead to fetal effusions [51–54]. The most commonly associated tachyarrhythmias are supraventricular tachycardia and atrial flutter [51–53, 55]. Less common tachyarrhythmias such as long QT syndrome leading to ventricular tachycardia or torsades de pointes, and ultimately NIHF, have also been described [56]. Both tachyarrhythmias and bradyarrhythmias may also result from structural abnormalities affecting cardiac conduction, such as heterotaxy syndromes [57, 58]. Fetal bradyarrhythmia is most commonly caused by congenital heart block, such as from anti-Ro/La Sjogren's syndrome-related antigen A and Sjogren's syndrome-related antigen B (SSA/SSB) antibodies associated with maternal autoimmune disease [59]. Genes associated with the development of the cardiac conduction system (e.g., *SCN5A* and *GATA4*) and the RASopathies (e.g., *HRAS*) may also underlie some fetal arrhythmias associated with fetal effusions [56, 60, 61].

Many skeletal dysplasias have been associated with fetal effusions, including achondrogenesis, osteogenesis imperfecta, osteopetrosis, thanatophoric dysplasia, short rib-polydactyly syndrome, asphyxiating thoracic dysplasia, and, rarely, achondroplasia [16, 30, 62–64]. The mechanism by which fetal effusions develop with skeletal dysplasias is not entirely clear. It has been proposed that hepatic enlargement occurs secondary to intrahepatic proliferation of blood cell precursors to compensate for a small bone marrow volume, which may lead to large vessel compression and fetal effusions [65].

Fetal masses are associated with effusions, sometimes resulting from a mass effect leading to impaired venous return and cardiac output or from highly vascular lesions leading to high-output cardiac failure. The most frequent pulmonary lesion associated with fetal effusions is congenital pulmonary airway malformation (CPAM), a cystic mass of disordered pulmonary parenchyma with abnormal proliferation of the bronchioles and lack of normal alveoli [66–68]. NIHF occurs in about 6%–7% of fetuses with CPAM, and the prognosis worsens with increasing size of the lesion (particularly when the CPAM volume ratio is ≥1.6) [66–68]. Additional lung lesions that confer risk of fetal effusions include bronchopulmonary sequestrations and congenital high airway obstruction syndrome [69, 70]. Fetal tumors and neoplastic diseases have also been associated with fetal effusions. In addition to thoracic masses, a variety of face and neck tumors, cardiac rhabdomyomas, sacrococcygeal teratomas, hepatoblastomas, vein of Galen aneurysms, and neuroblastomas have been reported with fetal effusions, and sacrococcygeal teratomas are among the most common of these [71–73].

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Other fetal structural anomalies, such as urinary and gastrointestinal abnormalities, are less common causes of fetal effusions. Congenital nephrotic syndromes have been reported to cause fetal effusions due to hypoproteinemia, with surviving infants at risk for massive proteinuria after birth and renal failure [74, 75]. NIHF has been reported to complicate approximately 4%–9% of pregnancies with congenital diaphragmatic hernia, likely in part the result of mass effect and impaired venous return, although a large number of genetic disorders may underlie these structural findings [76–78]. Other rare urinary and gastrointestinal abnormalities reported in association with fetal ascites or NIHF include midgut volvulus, meconium peritonitis, intestinal atresia, malrotation of the intestines, eventration, and prune belly syndrome [79–82]. Intra-abdominal masses may lead to fetal effusions due to obstruction of venous return, while gastrointestinal obstruction and infarction may lead to decreased colloid osmotic pressure due to protein loss [83]. Finally, fetal effusions have been reported with hepatic disorders such as fibrosis and cirrhosis, sometimes in the setting of underlying genetic disorders, such as Gaucher disease or trisomy 21 [84, 85].

2.2.3 | Fetal anemias

Fetal anemia arising from causes other than red blood cell alloimmunization can lead to one or more fetal effusions. Examples include inherited hematological disorders such as alpha thalassemia; acquired conditions such as fetal-maternal hemorrhage; infections such as parvovirus; and fetal or placental masses such as chorioangiomas. The most common inherited hematological disorder leading to fetal effusions is alpha thalassemia. This autosomal recessive disorder is common in Southeast Asian populations, where it accounts for 28%–55% of pregnancies with NIHF [46, 47]. Individuals of Southeast Asian, Filipino, and Mediterranean ancestries who are alpha thalassemia carriers often have deletions of two alpha globin genes (*HBA1* and *HBA2*) on one allele, increasing the risk of hemoglobin Bart syndrome in a fetus, which occurs when inactivated copies of all four alpha globin genes are inherited [86]. Hemoglobin Bart syndrome is marked by the presence of Bart's hemoglobin (an ineffective oxygen carrier), resulting in severe intrauterine hypoxia, fetal effusions, and, usually, fetal demise in the absence of intrauterine transfusions [87]. Other genetic disorders that can lead to fetal anemia and effusions include Diamond–Blackfan anemia, dehydrated hereditary stomatocytosis, and congenital dyserythropoietic anemias, among others [16, 88–90].

Severe fetal anemia resulting from fetal-maternal hemorrhage can lead to hypovolemia, fetal effusions, and death. Fetal-maternal hemorrhage may occur as either an isolated acute event or as a chronic, ongoing process [91, 92]. A Kleihauer-Betke stain will show the presence of fetal cells in the maternal peripheral blood, and flow cytometry can estimate the volume of fetal blood loss. If fetal-maternal hemorrhage is present, diagnosis is important because delivery or, in select situations, intrauterine transfusion may be indicated [93, 94].

2.2.4 | Structural abnormalities in the placenta or umbilical cord

Placental and umbilical cord lesions that have been associated with one or more fetal effusions include chorioangioma, choriocarcinoma, angiomyxoma, umbilical vein aneurysm, and umbilical vein thrombosis [72, 95–97]. Placental chorioangiomas are the most commonly reported, typically as a single lesion but occasionally as multiple lesions [98]. Large chorioangiomas can act as high-volume arterio-venous shunts and lead to high-output cardiac failure, with some evidence suggesting increased risk with chorioangiomas of 4–5 cm or larger [99–101].

2.2.5 | Infectious etiologies

Congenital infections are estimated to account for approximately 7%–8% of all pregnancies with NIHF [24, 30]. Fetal effusions have been reported in association with a number of viral, bacterial, and parasitic infectious diseases, including parvovirus, cytomegalovirus, syphilis, and toxoplasmosis [102–105]. Parvovirus is the most common infectious cause of NIHF. In the fetus, the virus has a predilection for erythroid progenitor cells, leading to inhibition of erythropoiesis and subsequent anemia [106, 107]. The risk of a poor outcome for the fetus is greatest when the congenital infection occurs before 20–24 weeks of gestation [108–110]. If infected, the risk of developing NIHF is up to 12%, and the overall risk of fetal death has been reported to range from 5% to 11% [108, 110]. The resulting anemia is often transient, and intrauterine transfusion can support a fetus through parvovirus-induced aplastic crisis. Less commonly reported viral and parasitic infections associated with fetal effusions include varicella zoster virus, enterovirus, herpes simplex type 1, human herpesvirus 6, respiratory syncytial virus, trypanosomiasis, and congenital lymphocytic choriomeningitis virus [111–116]. Such infections may cause fetal effusions due to anemia, anoxia, endothelial cell damage, increased capillary permeability, or myocarditis.

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2.2.6 | Complications of monochorionic twin pregnancies

TTTS results from an imbalance in blood flow caused by anastomoses in the placentas of monochorionic twin pregnancies. TTTS is covered in a separate Consult in further detail [117]. In pregnancies with more advanced (stage IV) TTTS, one or both twins may develop NIHF, although the recipient twin is more commonly affected, due to hypervolemia and increased central venous pressure [117]. Another complication of monochorionic twinning that may result in NIHF is twin-reversed arterial perfusion sequence, which can be treated with umbilical cord ablation of the acardiac twin [118, 119].

2.3 | What is the appropriate evaluation for NIHF?

Evaluation of the fetus for evidence of effusions or other anomalies is a routine component of a complete obstetrical ultrasound examination [120]. Once one or more fetal effusions are detected, the diagnostic challenge is to establish the etiology and determine the appropriate management, including any available therapy. Figure 2 outlines the various steps in the evaluation of a pregnancy with one or more fetal effusions. For pregnancies with one fetal effusion, it is reasonable to follow the same approach as for the diagnostic evaluation for multiple effusions (Figure 2), given the overlap in underlying etiologies and the importance of establishing a diagnosis [12, 14–19]. It is especially important to identify potentially treatable conditions and genetic disorders with a risk of recurrence in future pregnancies. Importantly, even if a structural anomaly is identified on prenatal imaging, a genetic disorder may explain both the anomaly and the fetal effusions. Genetic counseling is an integral part of the management plan for any patient with fetal effusions.

Evaluation of a fetus with one or more fetal effusions begins with a thorough family, medical, and obstetrical history to identify any risk of inherited genetic disorders, as well as infectious exposures, trauma, and other relevant events. Any laboratory studies completed to date should be thoroughly reviewed (Figure 2). The maternal blood type and Rh(D) antigen status are assessed as part of routine prenatal care, and an indirect Coombs test is performed to evaluate for circulating red blood cell antibodies. Even if the indirect Coombs test was previously negative, it should be repeated. The complete blood count and hemoglobin electrophoresis results should be reviewed to determine whether there is an increased risk of alpha thalassemia. If the red blood cell mean corpuscular volume is near or above 80 fL and hemoglobin electrophoresis results are normal, targeted testing with sequencing and deletion/duplication analysis for alpha thalassemia is indicated. Results of carrier screening panels for the biological parents should be reviewed. Serologic test results for syphilis should be reviewed and repeated with a new diagnosis of fetal effusions [103]. A Kleihauer-Betke stain or flow cytometry to assess for fetal-maternal hemorrhage is indicated, particularly in the setting of elevated middle cerebral artery (MCA) Doppler measurements (≥1.5 multiples of the median), suspected placental abruption, or maternal trauma.

When fetal effusions are diagnosed, a detailed sonographic evaluation should include a survey for abnormalities of the fetus, umbilical cord, or placenta; assessment of the MCA peak systolic velocity; and estimation of fetal growth and amniotic fluid volume [65]. Fetal cardiac anomalies are common in pregnancies with fetal effusions, and thus, fetal echocardiography should be performed [11, 28, 121]. MCA Doppler studies are important to evaluate for fetal anemia, with percutaneous umbilical cord blood sampling for confirmation in the setting of an elevated peak systolic velocity [122]. As structural anomalies may be seen in the setting of some inherited fetal anemias (e.g., limb anomalies or orofacial clefting with Diamond–Blackfan anemia) [123], MCA Doppler measurements should generally be performed even when anatomic abnormalities are observed.

CMA can detect many clinically relevant copy number variants not detectable by karyotype [124, 125], and it has become the standard of care in the setting of fetal anomalies [125]. However, it is important to note that karyotype is still needed to demonstrate a structural rearrangement as the origin of unbalanced genetic material, which can have important recurrence risk implications. Two small retrospective reviews of pregnancies with NIHF did not identify a significant incremental diagnostic yield of CMA over karyotype [34, 126]. Cell-free DNA (cfDNA) screening for aneuploidies should be considered when diagnostic testing is declined, as well as serum titers for parvovirus, cytomegalovirus, and toxoplasmosis [102, 104]. However, cfDNA screening is currently used for a limited number of conditions, and its results require diagnostic confirmation. Likewise, serum titers vary in performance and ability to accurately diagnose a suspected infection [127]. **We recommend fetal diagnostic testing for all pregnancies when one or more fetal effusions are detected; this testing should include CMA with or without karyotype. When infectious etiologies are part of the differential diagnosis, polymerase chain reaction (PCR) studies should also be performed (grading of recommendations assessment, development, and evaluation [GRADE] 1C).**

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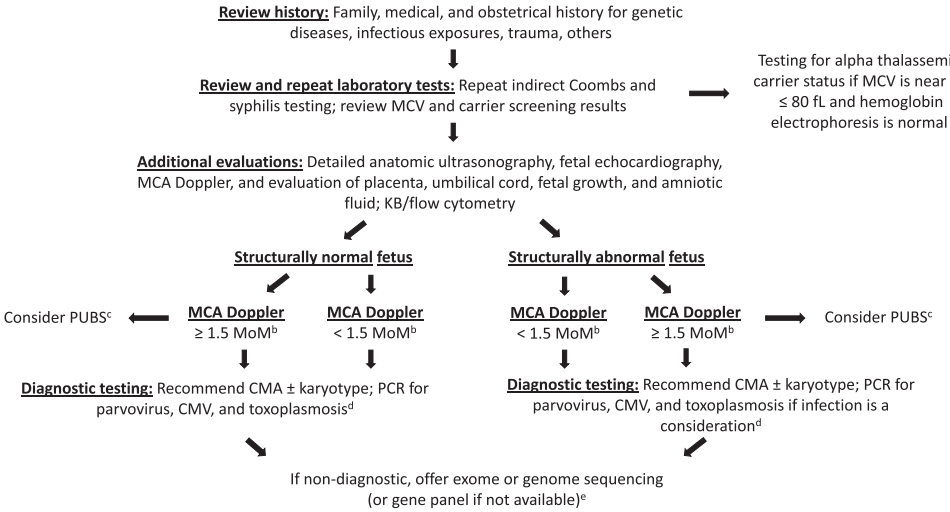


FIGURE 2 Diagnostic evaluations for non-immune hydrops fetalis and non-immune hydrops fetalis spectrum.[a] CMA, chromosomal microarray analysis; CMV, cytomegalovirus; fL, femtoliters; KB, Kleihauer-Betke test; MCA, middle cerebral artery; MCV, mean corpuscular volume; MoM, multiples of the median; PCR, polymerase chain reaction; PUBS, percutaneous umbilical cord blood sampling. [a]These evaluations are also reasonable for single fetal effusions suspected to be part of a more systemic process (non-immune hydrops fetalis spectrum). Additionally, while single fetal fluid collections such as a urinoma may result from a ruptured kidney or bladder, rather than from a more systemic process, a genetic evaluation should still be considered. [b]Perform middle cerebral artery Doppler regardless of whether fetal anatomy is structurally normal or abnormal. [c]Percutaneous umbilical cord blood sampling can be diagnostic of fetal anemia, and additional laboratory evaluations obtained from this procedure such as a blood smear can be helpful, for example, when a rare hereditary anemia is suspected. [d]In some circumstances, work-up with CMA ± karyotype may take place concurrently with exome or genome sequencing, such as in situations of time urgency or suspected greater diagnostic yield of exome or genome sequencing. If diagnostic testing with amniocentesis is declined, consider serum genetic screening for aneuploidies and serum testing for parvovirus, cytomegalovirus, and toxoplasmosis. If there is a family history of a genetic disorder that increases risk of fetal effusions or other relevant anomalies, a testing strategy is recommended for that specific genetic disorder. [e]If exome or genome sequencing is not available or feasible, a gene panel may instead be considered. Gene panels may be hydrops panels, RASopathy panels, metabolic panels, hereditary anemia panels, or others as appropriate.

If CMA or karyotype or both do not yield a diagnosis, next-generation sequencing (either exome or genome sequencing) should be offered, unless different testing strategies are indicated based on details of the history, fetal abnormalities, or other factors. For example, when there is a family history of a known genetic disorder that increases the risk of fetal effusions or the biological parents are carriers of a genetic disorder associated with fetal effusions, further testing should address these specific disorders. Several recent studies have demonstrated that exome sequencing will detect a single-gene disorder in at least one third of pregnancies with otherwise unexplained NIHF [40, 128–131]. RASopathies such as Noonan syndrome are the most common single-gene disorders underlying NIHF and single fetal effusions; other genetic disorders in the differential diagnosis include inborn errors of metabolism, other congenital lymphatic anomalies, fetal akinesia syndromes, musculoskeletal disorders, and hereditary anemias, among others (Table 2). While a variety of targeted gene panels test for some of the genes associated with NIHF, gene panels provide more limited genetic analysis and fail to detect 38%–89% of diagnoses underlying fetal effusions that are identifiable with exome sequencing [132]. A cost-effectiveness analysis further demonstrated that exome sequencing is more cost-effective than gene panels for one or more fetal effusions at all gestational ages [133].

Although exome and genome sequencing are typically performed after CMA that does not yield a diagnosis, in some circumstances, it may be appropriate to pursue genomic sequencing concurrently with CMA or karyotype. Such circumstances may include time constraints that require urgent pregnancy management decisions; a low risk of aneuploidy, such as with low-risk cfDNA screening results; or strong suspicion of a single-gene disorder. Based on current but very limited data, the incremental diagnostic yield of genome sequencing (which evaluates nearly the entire genome) over exome sequencing (which evaluates only the protein-coding regions) is small [134]. However, the turnaround time for genome sequencing is often faster than for exome sequencing, and smaller amounts of DNA are required. As such, either exome or genome sequencing is reasonable based on availability and patient preferences. Details of fetal structural abnormalities and medical history should be provided to the performing laboratory to inform variant interpretation

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with exome or genome sequencing, as such information has been shown to improve accuracy [131, 135]. There is, unfortunately, broad inequity in the ability to access these tests; there are also limitations in insurance coverage and often substantial out-of-pocket costs. When exome or genome sequencing is not feasible, gene panels should be offered, although even these are not uniformly accessible. **We recommend that exome or genome sequencing be offered in pregnancies with NIHF or NIHF spectrum following CMA or karyotype that does not yield a diagnosis and in the absence of another suspected etiology. If the risk of aneuploidy is low or a single-gene disorder is strongly suspected, offering exome or genome sequencing concurrently with CMA is reasonable (GRADE 1C)**.

Finally, perinatal laboratory and pathology evaluations are important considerations and may identify findings that help to determine the etiology of the fetal effusions. Existing studies on the incremental yield of pathology examination for NIHF are limited and largely predate contemporary genetic testing [136, 137]. However, fetal or neonatal autopsy can confirm the presence of anomalies or identify anomalies not detected in utero; fetal laboratory tests from procedures such as umbilical cord blood sampling or thoracentesis can demonstrate important findings, such as atypical red blood cell morphology or increased lymphocyte cell counts, respectively; and placental pathology can confirm infections, chorioangiomas, and other relevant findings [43, 136–138].

2.4 | What maternal risks are associated with NIHF?

Mirror syndrome is a complication in which the pregnant individual develops a form of preeclampsia with or without edema, which can "mirror" the hydropic fetus. Mirror syndrome is reported to occur in 8%–38% of all pregnancies with NIHF, although these estimates are limited by small numbers in most series [139–142]. One study raised the possibility of different risks of mirror syndrome according to the underlying etiology of NIHF, although there are limited data supporting this hypothesis [142].

Mirror syndrome is thought to represent a form of preeclampsia and is characterized by edema in approximately 90%, hypertension in 36%–60%, and proteinuria in 40%–64% of affected patients [140–142]. Additional associated findings may include headache, visual disturbances, oliguria, and abnormal laboratory values (such as abnormal liver function, elevated creatinine, or low platelets) [140–142]. Preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome have also been reported to manifest as mirror syndrome. Smaller series and a systematic review have reported frequent major morbidities with mirror syndrome, including pulmonary edema in 8%–36% of affected pregnancies, postpartum hemorrhage in 44%–50%, need for blood transfusion in 19%, and intensive care unit admission in 13% [140, 141, 143]. However, a large series based on statewide birth data reported lower frequencies of these complications: pulmonary edema in 1.5%, postpartum hemorrhage in 8%, and need for blood transfusion in 4% [139]. Limitations of the existing literature include a lack of diagnostic criteria for mirror syndrome and historical variation in the diagnostic criteria for preeclampsia, leading to variability across studies.

Resolution of mirror syndrome occurs with delivery, although there are case reports of resolution of hydrops and mirror syndrome after fetal interventions for arrhythmia, hydrothorax, parvovirus, and bladder obstruction [141, 142, 144–149]. Other case reports have documented resolution of mirror syndrome following spontaneous demise or induced fetal demise of a hydropic fetus [150, 151]. Similar imbalances of angiogenic and antiangiogenic factors described in preeclampsia have also been observed in pregnancies with mirror syndrome, with correction following intervention to treat the NIHF [146, 148, 152]. However, there are limited data regarding the likelihood of resolution of mirror syndrome with fetal intervention or the safety of the pregnant individual with this approach. **We recommend that all patients who develop mirror syndrome in the setting of NIHF receive individualized counseling about delivery or abortion care; expectant management should be reserved only for rare circumstances, after counseling about the maternal risks and shared decision-making (GRADE 1C)**.

2.5 | What other obstetrical complications are associated with NIHF?

Polyhydramnios and preterm birth occur frequently with NIHF, with reported incidences as high as 59% and 86%, respectively [11, 139, 153, 154]. Median gestational ages at delivery range from 32 to 36 weeks in contemporary cohorts, including both spontaneous preterm labor and medically indicated delivery [3, 28, 63, 153, 154]. Among the patients delivered preterm in a recent retrospective series, 38% followed spontaneous preterm labor or preterm premature rupture of membranes, 19% had maternal indications for delivery (primarily preeclampsia), and 44% had fetal indications for delivery (either non-reassuring antenatal testing or worsening fetal effusions) [153]. The management of polyhydramnios [155], preterm premature rupture of membranes [156], and preterm birth [157] are

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covered in separate Society for Maternal-Fetal Medicine Consults and American College of Obstetricians and Gynecologists Practice Bulletins, and considerations about timing of delivery and fetal and neonatal interventions in the setting of NIHF are discussed in more detail elsewhere in this Consult. (See Section 2.10: *What is the optimal timing of delivery in pregnancies complicated by NIHF?*)

2.6 | What is the prognosis for NIHF?

Approximately 15%–21% of all pregnancies with NIHF result in spontaneous abortion or stillbirth [3, 126, 154, 158]. The risk of spontaneous loss is higher in the setting of fetal effusions or cystic hygroma in the first and second trimesters, with reports of spontaneous loss occurring in up to 62%–86% in some series [121, 159–161]. This greater risk is likely influenced by the higher prevalence of aneuploidy among these early presentations and is anticipated to be higher with decreased access to abortion. In most series, overall survival among liveborn neonates with NIHF ranges from 36% to 68% [28, 63, 121, 158, 162–164].

The risks of neurologic impairment and major morbidity in liveborn infants among all pregnancies complicated by NIHF are estimated at up to 48% and 39%, respectively [28, 63, 121, 158, 162–164]. Among live births, the prognosis of NIHF has been reported to depend on the underlying etiology as well as additional factors, such as the presence of other anomalies or genetic diagnoses, number and types of fetal effusions, spontaneous improvement in fetal effusions, response to in utero interventions, gestational age at detection of NIHF, gestational age at delivery, birthweight, resuscitation required at birth, low serum albumin level, and the presence of severe acidemia [28, 63, 121, 158, 162–164]. NIHF resulting from lymphatic dysplasia, tachyarrhythmias, parvovirus, and lung masses has been reported to have more favorable outcomes, including long-term neurodevelopmental outcomes, while pregnancies with NIHF associated with trisomy 13 or 18, inborn errors of metabolism, and cardiac anomalies are at greater risk of morbidity and mortality [28, 63, 121, 158, 162–166].

Fetuses with NIHF amenable to in utero interventions may demonstrate improved perinatal outcomes. Examples include when thoracentesis is performed to treat a primary chylothorax or when in utero transfusions are administered for fetal anemia due to alpha thalassemia major [167, 168]. Outcomes have generally been reported as favorable following intrauterine transfusions for fetuses with NIHF due to parvovirus, with an 85% chance of survival among those receiving transfusions and poorer outcomes without transfusions [109, 169]. However, one small series raised concern about the risk of long-term neurodevelopmental delay [170], perhaps due to the impact of hydrops or a direct consequence of the parvovirus infection, severe anemia, or the transfusions. Two studies examining the outcomes of fetal supraventricular tachycardia suggest that persistent postnatal arrhythmia is more likely with later gestational age at diagnosis but not with the presence of NIHF alone [53, 171].

Counseling about anticipated outcomes should be individualized to each pregnancy with NIHF, given the range in underlying etiologies and other factors, such as gestational age at delivery, which can affect prognosis. Consultation with a neonatologist, geneticist, or other relevant pediatric subspecialists can help clarify expectations about anticipated postnatal prognosis and important decision points, such as the degree of interventions desired after birth. Other understudied prognostic considerations include the pregnancy course by underlying etiology of the NIHF, the long-term impact of NIHF on the postnatal prognosis for specific genetic disorders, and the ultimate quality of life.

2.7 | What is the management of NIHF?

Pregnancy management decisions should be based on the preferences of the pregnant individual, any obstetrical complications or major comorbidities, gestational age at which NIHF develops, known or suspected etiology of NIHF, availability of fetal or neonatal interventions, and other clinical considerations. Those with fetal effusions or NIHF that could benefit from fetal therapy should be offered referral to a specialized center as appropriate. Counseling should acknowledge the spectrum of prognoses that exist according to the underlying etiology. The gestational age at which a fetus with NIHF has the potential to survive after delivery depends on the unique clinical characteristics of each pregnancy. Comprehensive multidisciplinary counseling, including representatives from maternal-fetal medicine and neonatology, is important to determine optimal management options for continuing pregnancies, such as mode of delivery, the gestational age at which neonatal resuscitation would be offered, the degree of neonatal resuscitation desired, plans for relevant neonatal interventions, and options for palliative care.

Due to the increased risk of preeclampsia (e.g., with mirror syndrome) [139–143], in continuing pregnancies with persistent NIHF, consideration should be given to serial evaluations of maternal blood pressure, monitoring for the development of any preeclampsia symptoms, and periodic laboratory assessments. Patients should also be counseled about the increased risks of preterm birth [153, 154] and cesarean delivery [11, 28, 166, 169] in pregnancies with NIHF. **Given the associated maternal risks, we recommend that all patients with pregnancies complicated**

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TABLE 3 Example of therapies for selected etiologies of non-immune hydrops fetalis and single fetal effusions in continuing pregnancies.

Etiology	Therapy[a]	Additional considerations
Fetal tachyarrhythmia, supraventricular tachycardia, atrial flutter, or atrial fibrillation	Maternal administration of antiarrhythmic medication(s)	Treatment with antiarrhythmic medication unless risks associated with delivery are considered less than those of continuing the pregnancy or the medication, or unless there is maternal or obstetrical contraindication
Fetal anemia due to infection, fetomaternal hemorrhage, hereditary anemia, or other	Fetal blood sampling followed by intrauterine transfusion if indicated	Intrauterine transfusion if anemia is confirmed, unless risks associated with delivery are considered less than those with the procedure
Fetal hydrothorax, chylothorax, or large pleural effusion(s)	Needle drainage of fetal effusion or placement of thoracoamniotic shunt	Consider drainage or thoracoamniotic shunt placement when the goal is prolongation of pregnancy or if drainage might confer benefit prior to delivery
Fetal CPAM	Maternal administration of corticosteroids for larger CPAMs, surgical interventions such as cyst aspiration or thoracoamniotic shunt for large cysts	Corticosteroids are most efficacious for microcystic lesions, and a repeat course of corticosteroids can be considered for larger lesions
Twin-reversed arterial perfusion sequence	Percutaneous radiofrequency or microwave ablation	Offer percutaneous radiofrequency or microwave ablation of the acardiac twin

Abbreviation: CPAM, congenital pulmonary airway malformation.

[a]Additional emerging fetal therapies may be available through clinical trials at select tertiary care or fetal centers.

by NIHF receive individualized counseling and be offered all management options, including abortion care (GRADE 1C).

2.8 | What are the fetal therapy options available for NIHF?

Examples of some of the etiologies of NIHF for which fetal therapy is currently available are listed in Table 3. Nuances of these fetal therapies are beyond the scope of this document, but examples include medications such as antiarrhythmic agents, intrauterine transfusion(s) for fetal anemia, and corticosteroids for CPAM. This list is not comprehensive but rather offers examples of interventions that may be considered for some pregnancies. The strength of the evidence for effectiveness of each intervention varies substantially with different conditions and therapies. Some therapies are also offered in pregnancies identified as being at risk for progression, such as drainage of a unilateral large pleural effusion, with the expectation that the prognosis worsens if additional fetal effusions develop [172, 173]. Counseling for patients who are continuing pregnancies with NIHF that are amenable to fetal therapy should include a discussion of potential risks, benefits, and alternatives, taking into consideration the severity of the underlying condition, the anticipated response to the intervention, any maternal risks, and the gestational age at possible intervention. Additional emerging fetal therapies may be available through clinical trials at select fetal centers. An increasingly relevant consideration is whether certain fetal interventions should be pursued in the setting of a known fetal genetic disease. There is a lack of evidence to guide such decisions, but because the severity of genetic diseases and individual values and preferences vary so widely, clinicians and patients should engage in shared decision-making based on the unique details of each pregnancy and with input from relevant subspecialists in maternal-fetal medicine, genetics, pediatric surgery, neonatology, and other areas.

2.9 | When is antepartum fetal surveillance appropriate in NIHF?

Antepartum surveillance is generally used in the setting of maternal or pregnancy complications associated with an increased risk for fetal demise and when findings from surveillance will assist with delivery decisions. For NIHF, antepartum surveillance has not been shown to improve perinatal outcomes, and decisions about whether and when to initiate surveillance should be individualized [174]. There are no trials or observational series on the utility of antepartum surveillance in the setting of NIHF on which to base recommendations. Whether an individual pregnancy with NIHF will benefit from surveillance depends on the etiology and expected prognosis, the gestational age, whether neonatal resuscitation

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will be pursued, and whether urgent cesarean delivery would be performed. Multidisciplinary counseling with maternal-fetal medicine, neonatology, and other relevant subspecialists should be performed whenever possible to determine the answers to such questions. While data are lacking, it is reasonable to employ surveillance once the pregnancy has reached a gestational age at which neonatal interventions would be offered and are desired by the patient. In such pregnancies, deterioration of the fetal status or worsening sonographic findings of hydrops might prompt delivery or other changes to clinical management.

2.10 | What is the optimal timing of delivery in pregnancies complicated by NIHF?

There are no clinical trials of delivery timing in the setting of NIHF on which to base recommendations. Many hydropic fetuses die in utero, and up to 86% of pregnancies with NIHF are delivered preterm following spontaneous preterm labor or for fetal or maternal indications [11, 126, 153, 154]. However, there is no clear evidence that elective preterm delivery for all pregnancies with NIHF would improve postnatal outcomes, and in several retrospective series, preterm birth has been shown to be a poor prognostic factor for survival [28, 153, 163, 164]. Based on expert opinion, in the setting of new or worsening NIHF, delivery might be reasonable for a pregnancy that has reached 34 weeks of gestation to balance the risks of in utero demise and prematurity. Further prolongation of the pregnancy may be possible for more stable scenarios, but clear data to support an optimal gestational age for delivery are lacking. **We recommend that the timing of delivery be individualized for each pregnancy with NIHF and that preterm delivery be reserved for obstetrical indications such as preeclampsia or mirror syndrome, preterm labor or premature rupture of membranes, or new or worsening NIHF, or when the overall maternal or fetal risks of continued management are expected to outweigh those of delivery (GRADE 1C)**. Additionally, in scenarios where the prognosis is considered to be poor or life-limiting and patients wish to pursue abortion or palliative care, preterm induction of labor should be offered.

2.11 | Should antenatal corticosteroids or tocolytics be given for fetal benefit in pregnancies with NIHF?

There are no studies designed to specifically address the utility of antepartum corticosteroid therapy in the setting of NIHF or the gestational ages at which to administer corticosteroids. One retrospective series that evaluated multiple factors associated with survival found that corticosteroid administration prior to delivery reduced the risk of neonatal mortality, while several other series concluded that survival was not improved among those who received corticosteroids [28, 162, 164, 175, 176]. These conflicting findings are likely due to the overall high baseline risk of mortality as well as the heterogeneous underlying pathophysiologies among infants with NIHF. While there is limited available evidence for the use of antenatal corticosteroids in pregnancies complicated by NIHF, **we recommend antenatal corticosteroids for continuing pregnancies with NIHF when preterm delivery is anticipated within 7 days, if neonatal resuscitation is desired and would be offered (GRADE 1C)**.

Similarly, there are no studies designed to specifically address the utility of tocolytic agents in the setting of NIHF. In the absence of data, the use of tocolytic agents may be limited for the purpose of completing antenatal corticosteroids or periprocedure when a fetal procedure is performed and prolongation of pregnancy is the goal [177].

2.12 | What is the optimal mode of delivery with NIHF?

Up to 85% of pregnancies with NIHF are delivered by cesarean [11, 28, 163, 164]. However, unless otherwise contraindicated, vaginal delivery is appropriate in pregnancies without evidence of acute fetal deterioration or if a decision has been made to provide palliative care. While no clinical trials exist to guide the mode of delivery for NIHF, a large retrospective study did not demonstrate a significant difference in risk of neonatal mortality according to the mode of delivery [11]. Until further evidence exists, the mode of delivery for each affected pregnancy should be individualized. Prior to delivery of the hydropic fetus, consideration can be given to whether drainage of a fetal effusion (such as a large pleural effusion or ascites) will prevent dystocia or improve the efficacy of neonatal resuscitative efforts. Rarely, effusions can be so large as to pose a risk for trauma to the fetus during delivery, and the risk of dystocia should be considered and discussed. **We recommend that cesarean delivery be performed for standard obstetrical indications in the setting of NIHF when postnatal resuscitation and life-supporting care are planned for the neonate (GRADE 1C)**.

2.13 | Where should delivery occur?

If NIHF is potentially amenable to postnatal treatment or if the etiology is not known, delivery at a center with a Level III or IV neonatal intensive care unit that has the capability

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to stabilize and treat critically ill neonates may be required. Transfer of care for the pregnant patient prior to delivery should be considered in such scenarios. However, in situations where a family has selected abortion or palliative care for the neonate, delivery at such a center may not be necessary so long as the desired services are available.

3 | CONCLUSION

NIHF is heterogeneous and can result from a large number of underlying fetal genetic diseases, congenital anomalies, congenital infections, tumors of the placenta, and other etiologies. From a diagnostic perspective, many underlying etiologies can present along a spectrum with one or more fetal effusions, which may be referred to as "NIHF spectrum." In the presence of one or more fetal effusions, a comprehensive fetal anatomic survey and diagnostic testing should be offered to determine the etiology of NIHF, including evaluations for genetic diseases, congenital anomalies, infections, placental tumors, and other disorders. Efforts to improve access to prenatal exome and genome sequencing are essential. Counseling about expected prognosis is best individualized, and multidisciplinary counseling can facilitate comprehensive clinical management plans. Given the maternal and fetal risks associated with NIHF and its causes, individuals should have access to all reproductive options, including abortion care and delivery with palliative postnatal care. For continuing pregnancies, fetal treatments may be available depending on the underlying etiology, and counseling about fetal interventions should include a discussion of the potential risks, benefits, and alternatives. Timing of delivery should be individualized for each affected pregnancy, with preterm birth reserved for obstetrical indications such as mirror syndrome, preterm labor or premature rupture of membranes, or new or worsening NIHF, or when the overall risks of continued expectant management outweigh those of delivery.

Summary of recommendations.[a]

Number	Recommendation	GRADE
1	We recommend fetal diagnostic testing for all pregnancies when one or more fetal effusions are detected; this testing should include CMA with or without karyotype. When infectious etiologies are part of the differential diagnosis, PCR studies should also be performed.	1C
2	We recommend that exome or genome sequencing be offered in pregnancies with NIHF or NIHF spectrum following CMA or karyotype that does not yield a diagnosis and in the absence of another suspected etiology. If the risk of aneuploidy is low or a single-gene disorder is strongly suspected, offering exome or genome sequencing concurrently with CMA is reasonable.	1C
3	We recommend that all patients who develop mirror syndrome in the setting of NIHF receive individualized counseling about delivery or abortion care; expectant management should be reserved only for rare circumstances, after counseling about the maternal risks and shared decision-making.	1C
4	Given the associated maternal risks, we recommend that all patients with pregnancies complicated by NIHF receive individualized counseling and be offered all management options, including abortion care.	1C
5	We recommend that the timing of delivery be individualized for each pregnancy with NIHF and that preterm delivery be reserved for obstetrical indications such as preeclampsia or mirror syndrome, preterm labor or premature rupture of membranes, or new or worsening NIHF, or when the overall maternal or fetal risks of continued management are expected to outweigh those of delivery.	1C
6	We recommend antenatal corticosteroids for continuing pregnancies with NIHF when preterm delivery is anticipated within 7 days, if neonatal resuscitation is desired and would be offered.	1C
7	We recommend that cesarean delivery be performed for standard obstetrical indications in the setting of NIHF when postnatal resuscitation and life-supporting care are planned for the neonate.	1C

Abbreviations: CMA, chromosomal microarray analysis; GRADE, grading of recommendations assessment, development, and evaluation; NIHF, non-immune hydrops fetalis; PCR, polymerase chain reaction.

[a]See the Supporting Information for the evidence summary table.

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Society for Maternal-Fetal Medicine grading of recommendations assessment, development, and evaluation (GRADE) system [178, 179].

Grade of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Consistent evidence from well-performed, randomized controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits appear to outweigh risks and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to influence confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.
Best practice	Recommendation in which either (i) there is an enormous amount of indirect evidence that clearly justifies a strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize) or (ii) a recommendation to the contrary would be unethical.		

Note: Adapted from Guyatt et al. [178].

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Guidelines.

The content of this document reflects the national and international guidelines related to non-immune hydrops fetalis.

Organization	Title	Year of publication
American College of Obstetricians and Gynecologists	Practice Bulletin No. 151: Cytomegalovirus, Parvovirus B19, Varicella Zoster, and Toxoplasmosis in Pregnancy [127]	2015
American College of Obstetricians and Gynecologists	Practice Bulletin No. 171: Management of Preterm Labor [177]	2016
American College of Obstetricians and Gynecologists	Committee Opinion No. 682 Summary: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology [125]	2016
American College of Obstetricians and Gynecologists	Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234 [157]	2021
American College of Obstetricians and Gynecologists	Indications for Outpatient Antenatal Fetal Surveillance: ACOG Committee Opinion, Number 828 [174]	2021
American Institute of Ultrasound in Medicine, American College of Radiology, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, and Society of Radiologists in Ultrasound	Practice Parameter for the Performance of Standard Diagnostic Obstetric Ultrasound Examinations [120]	2018
Society for Maternal-Fetal Medicine	Society for Maternal-Fetal Medicine Consult Series #46: Evaluation and Management of Polyhydramnios [155]	2018
Society for Maternal-Fetal Medicine	Society for Maternal-Fetal Medicine Consult Series #64: Systemic Lupus Erythematosus in Pregnancy [59]	2023
Society for Maternal-Fetal Medicine	Society for Maternal-Fetal Medicine Consult Series #72: Twin-Twin Transfusion Syndrome and Twin Anemia-Polycythemia Sequence [117]	2024
Society for Maternal-Fetal Medicine	Society for Maternal-Fetal Medicine Consult Series #71: Management of Previable and Periviable Preterm Prelabor Rupture of Membranes [156]	2024

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