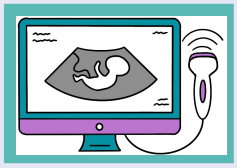
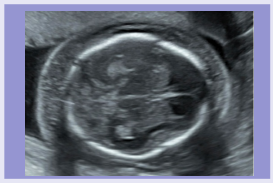
Society for Maternal-Fetal Medicine

Consult Series #75

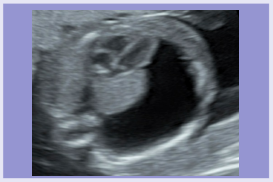
EVALUATION AND MANAGEMENT OF NON-IMMUNE HYDROPS FETALIS

Hydrops = the presence of abnormal fluid collections in 2+ fetal compartments

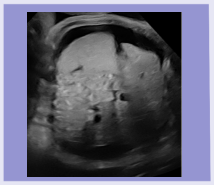




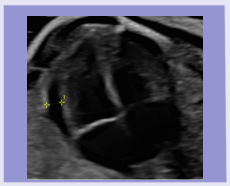
Generalized skin edema (>5mm)



Pleural effusion



Ascites



Pericardial effusion (>2-3 mm)

Non-immune hydrops fetalis (NIHF) = hydrops not caused by red cell alloimmunization

EVALUATION

Review history: Family, medical, and obstetrical history for genetic diseases, infectious exposures, trauma, others

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Review and repeat laboratory tests: Repeat indirect Coombs and syphilis testing; review MCV and carrier screening results → Testing for alpha thalassemia carrier status if MCV is near or ≤ 80 fL and hemoglobin electrophoresis is normal

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Additional evaluations: Detailed anatomic ultrasonography, fetal echocardiography, MCA Doppler, and evaluation of placenta, umbilical cord, fetal growth, and amniotic fluid; KB/flow cytometry

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Structurally normal fetus

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MCA Doppler ≥ 1.5 MoM[b] → Consider PUBS[c]

MCA Doppler < 1.5 MoM[b]

↓

Diagnostic testing: Recommend CMA ± karyotype; PCR for parvovirus, CMV, and toxoplasmosis[d]

Structurally abnormal fetus

Even if a structural anomaly is identified, a genetic disorder may explain both the anomaly and the fetal effusions

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MCA Doppler < 1.5 MoM[b]

MCA Doppler ≥ 1.5 MoM[b] → Consider PUBS[c]

↓

Diagnostic testing: Recommend CMA ± karyotype; PCR for parvovirus, CMV, and toxoplasmosis if infection is a consideration[d]

↓

If non-diagnostic, offer exome or genome sequencing (or gene panel if not available)[e]

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

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

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.

MATERNAL RISKS

Mirror Syndrome

The pregnant individual develops a form of preeclampsia with or without edema

Occurs in 8-38% of all pregnancies with NIHF

Associated findings:

- Edema
- Hypertension
- Proteinuria
- Headache
- Visual disturbance
- Oliguria
- Abnormal laboratory values

Resolution occurs with delivery
Case reports of resolution after fetal intervention

We recommend that all patients with mirror syndrome in the setting of NIHF receive 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

OBSTETRICAL COMPLICATIONS

Polyhydramnios 59%
Preterm birth 86%

PROGNOSIS

Counseling should be individualized given the range in underlying etiologies and other factors, such as gestational age at delivery

Spontaneous abortion/stillbirth with NIHF: 15-21%
Survival among liveborn neonates with NIHF: 30-68%
Risk of neurological impairment 48%
Risk of major morbidity 39%

Consultation with a neonatologist, geneticist, or other relevant pediatric subspecialists can help clarify expectations

MANAGEMENT

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

Consider serial evaluations for increased risk of preeclampsia

FETAL THERAPY OPTIONS

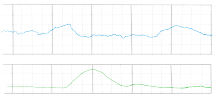
TABLE 3 Example of therapies for selected etiologies of non-immune hydrops fetalis and single fetal effusions in continuing pregnancies.

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.

ANTEPARTUM FETAL SURVEILLANCE



Has not been shown to improve perinatal outcomes, and decisions about whether and when to initiate surveillance should be individualized

ANTENATAL CORTICOSTEROIDS

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

DELIVERY TIMING

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

MODE OF DELIVERY

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

WHERE SHOULD DELIVERY OCCUR

If amenable to postnatal treatment or unknown etiology, delivery at a center with a Level III or IV neonatal intensive care unit may be required