# NON-IMMUNE HYDROPS FETALIS

**Miguel Arraz, Virginia Borobio, Joan Sabriá, Anna Goncé**

## 1. INTRODUCTION: DEFINITION AND IMPORTANCE OF HYDROPS

Hydrops is defined as the abnormal presence of serous fluid in at least two fetal compartments (pericardial effusion, pleural effusion, ascites, subcutaneous edema).

Polyhydramnios and increased placental thickness (>6 cm) are frequently associated. **The main classification** of hydrops is based on two groups of etiologies: **immune and non-immune.** Due to the widespread use of anti-D gamma globulin prophylaxis in recent decades, the majority of hydrops presenting nowadays are of non-immune origin (85-90%).

Non- immune hydrops (NIPH) is defined by the absence of circulating maternal antibodies against fetal erythrocytes. The frequency of occurrence of non-immune hydrops varies according to series from 1/1500 to 1/4000 deliveries.

Hydrops is always a serious situation and should therefore be studied and if possible treated in a tertiary center and by a multidisciplinary team. The prognosis is generally poor, although it depends on the etiology, the possibility of treatment and the gestational age. Mortality is high despite the fact that we have more and more tools available for a careful diagnosis and we can select the cases susceptible to intrauterine treatment. Otherwise, it is important to try to precise the diagnosis in order to be able to offer prenatal advice for future pregnancies. Even so, almost one in four cases remains undiagnosed.

The purpose of this clinical guide is to specify the steps to follow for the etiological diagnosis of hydrops and to offer intrauterine therapy if the pathology requires it. It is important to point out that cases requiring fetal therapy, from 16-18 weeks, are considered a medical emergency and require quick action.

## 2. ETIOLOGY

Hydrops is caused by an imbalance of fluid volume between the vascular and interstitial space and can be considered the final stage of fetal compensation processes.

The pathophysiological mechanism is different depending on the etiology:

- Primary cardiac failure (structural or functional abnormality, myocarditis or severe anemia).

- Cardiac failure due to overload/hyperdynamics (arteriovenous shunts, tumors, complications of monochorionic gestation).
- Venous return obstruction (compression at thoracic or, more rarely, abdominal level).
- Lymphatic drainage obstruction at thoracic/abdominal level.
- Decreased oncotic pressure (decreased albumin production in hepatic involvement in infections or increased excretion in congenital nephrotic syndrome).
- Increased capillary permeability (hypoxia/anoxia).

**The most frequent causes of HNI are:**

**2.1. Cardiovascular (35%):**

- **Structural:** Mainly anomalies of the right heart and venous return.
- **Functional:** Arrhythmias (tachycardia, flutter, bradycardia, A-V block), tumors, cardiomyopathies, anomalies that generate high output (chorioangioma, aneurysm of the vein of Galen, A-V fistulas, venous ductus agenesis with extrahepatic drainage, complications in monochorionic twin pregnancies (STFF, TAPS, TRAP).

**2.2. Chromosomal abnormalities (7-15%):** In first trimester hydrops, the incidence is up to 70%. Monosomy X or Turner syndrome is the most frequently associated.

**2.3. Structural malformations (14%):**

- Thoracic (6%)
- Musculoskeletal (3-4%)
- Nephrourinary (2-3%)
- Gastrointestinal (2%)

**2.4. Congenital infections (7-10%):** Parvovirus B19 is the most frequent (25% of 2nd and 3rd hydrops with normal fetal anatomy), followed by CMV and syphilis (it is essential to consider this infection especially in 3rd trimester hydrops due to an important global increase), and toxoplasma. More rarely, rubella, varicella, herpes simplex type I and II and enterovirus (Coxsackie B). Although very infrequent, it has also been described in lymphocytic choriomeningitis (Arenavirus) (rodent-borne infection), and also described after Zika virus infection.

**2.5. Hematologic alterations (10-17%):** Severe fetal anemia is a frequent cause of NIHF: feto-maternal hemorrhage, major alpha-thalassemia, anemia secondary to parvovirus B19 infection, glucose 6-phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) deficiency, and aplastic anemia (Blackfan-Diamond syndrome) or transient myeloproliferative disorders described in Down syndrome and congenital leukemia. Down syndrome and congenital leukemia.

**2.6. Lymphatic dysplasia (5%):** cystic hygroma, lymphedema syndromes.

**2.7. Genetic syndromes (5-10%):** Noonan syndrome and RASopathies are frequent causes of hydrops but there are multiple associated syndromes

**2.8. Fetal/placental tumors and arterio-venous malformations (2%):** teratoma, lymphagioma, neuroblastoma, hemangioma, placental chorioangioma, vein of Galen aneurysms, arterio-venous fistulas, etc.

**2.9. Metabolopathies (2%):**

- Dense Deposit Desease (DDD) (Lysosomal): Gaucher disease, GM1 gangliosidosis, Hurler syndrome, mucopolysaccharidosis I, II and VII, Nemann-Pick disease, Galactosialidosis, Farber disease, sialic acid storage disease and carnitine deficiency.
- Congenital hypoproteinemia.

**2.10. Unknown cause (15-20%).**

## 3. DIAGNOSIS AND STUDY

The ultrasound diagnosis of hydrops is simple. Hydrops is defined as the presence of accumulation of fluid in at least 2 extravascular spaces, usually characterized by the presence of generalized subcutaneous edema, pleural or pericardial effusion and/or ascites.

It is also often associated with placental edema and polyhydramnios. However, reaching the etiologic diagnosis of the process can be difficult and remains a challenge. Identification of the cause can be made in up to 55-60% prenatally and if postnatal study is added, the diagnosis can be made in 75-85% of cases. In a situation of hydrops fetalis, the patient should be referred to a tertiary center and should be attended by a multidisciplinary team. It is important to maximize the diagnostic possibilities to

distinguish the fetuses that are susceptible to treatment and, if not, to be able to assess the parents about the available options due to the associated poor fetal prognosis (legal termination of pregnancy or palliative treatment), and to provide advice regarding future pregnancies and the risk of recurrence. A hydropic fetus is in a decompensation phase and requires urgent and coordinated action aimed at identifying the cause, the possibility of treatment, viability and optimal timing of delivery.
To rule out immune hydrops we will perform a maternal blood test with FBC (Full Blood Count), group and Rh, indirect Coombs and irregular antibodies. If an immune hydrops is present, the alloimmunization protocol will be considered.

**3.1. Medical history:** ethnic origin (homozygous alpha-thalassemia more frequent in Southeast Asia), existence of consanguinity (more probability of recessive disorders), personal history: SLE, diabetes or previous pregnancy losses that could be related to metabolic errors or chromosomal abnormalities. Travel history or possible contact with infectious agents should be investigated. Parvovirus B19 and CMV infection is more frequent in teachers, day-care workers and mothers of children < 3 years of age. Risk behaviors for STIs. Primary and secondary syphilitic lesions may go unnoticed.

**3.2. Ultrasound:** which will try to investigate the causes and identify early tratable cases (some structural malformations, anemia and infection). We will rule out malformations (especially cardiovascular and thoracic). We will carefully look for ultrasound markers of infection such as microcephaly, ventriculomegaly and intracranial o hepatic calcifications.
We will also consider metabolopathies when hydrops is associated with IUGR, hypertrophic cardiomyopathy, hypomotility or akinesia, skeletal abnormality or hepatosplenomegaly.
It will include an **arterial and venous Doppler study** to assess the fetal status and the maximum velocity of the middle cerebral artery (PSV ACM >1.5 MoM has a high predictive value for severe anemia).
If there are signs of fetal anemia, we will propose a cordocentesis to check it. Previously, we will have blood prepared for a possible intrauterine transfusion, regardless of the lack of etiological or genetic diagnosis.

**3.3. Echocardiography.** It is mandatory to rule out structural abnormalities (more frequently if they present valvular involvement) or funcional abnormalities (arrhythmias, tumors, dysfunction, cardiomegaly, agenesis of DV with extrahepatic drainage).

**3.4. Maternal laboratory tests** will include complete blood count, blood group and Rh, irregular antibodies, serology: IgG and IgM for parvovirus B19, cytomegalovirus, toxoplasma, rubella (in the

absence of previous immunity), lupus (reagin and treponemal tests), and Zika if there is a history of epidemiological risk. The Kleihauer-Betke test will be requested to rule out significant fetomaternal hemorrhage. In selected cases, diabetes should be ruled out and, if non-filarial anemia is suspected, hemoglobin studies and investigation of G6PD deficiency should be performed. In the presence of fetal bradyarrhythmia, Ac anti-Ro/La that are present in some autoimmune diseases will be solicited.

**3.5. Amniocentesis** is a test that we will always perform. **QF-PCR and array-CGH** will be **requested**. Amniocentesis will be mandatory for the study of infections by **PCR techniques** for detection of viral, bacterial or parasitic DNA in LA (parvovirus B19, CMV, enterovirus, herpes simplex, arenavirus, treponema pallidum, toxoplasma and zika if epidemiological history of risk) and DNA will be saved for possible studies of some genetic and metabolic diseases. Likewise, **an exome study directed to a panel of genes involved in Hydrops-RASopathies and Noonan syndrome will be requested, in the absence of structural cause or anemia.**

At the same time, and in the event of suspicion of a possible metabolopathy, a biochemical study of diseases caused by metabolic errors in amniotic fluid will be performed. Fourteen types of lysosomal diseases associated with NIH have been described. In our center there is a relatively rapid protocol for the screening of 7 of them: Mucopolysaccharidosis I and VII, MGM1 gangliosidosis, Galactosidosis, Niemann-Pick type A, Farber's disease and sialic acid storage disease. In that case, 5-10 mL of extra AF will be obtained.

**3.6. Cordocentesis**, when gestational age allows it (>19-20 weeks) is a key test in the study of hydrops if **anemia and/or hematologic diseases** are suspected and should be performed early. If we have to perform it, we will requested QF-PCR and array-CGH, direct Coombs' test, full blood count, proteins, albumin and liver function test. Other studies will be performed selectively (by example: DNA studies in known metabolopathies, gene panel associated with hydrops-RASopathies and Noonan syndrome, DNA-PCR of infections in the absence of amniotic fluid). If intrauterine transfusion is planned, crossmatching blood should be available to avoid successive procedures. In selected cases (viable gestational age and easy access) and in the absence of other identified causes, transfusion may be considered even if the MCA velocity is normal, since in advanced stages of hydrops it may normalize despite the fetal anemia.

3.7. In selected cases, **aspiration of cavities with fluid accumulation** (pleural effusion, ascites) will be assessed to study the lymphocyte proportion, protein/albumin ratio and creatinine/ionogram

(ascites). In the absence of AF, PCR techniques can be performed to investigate viral or parasitic infection, as well as genetic studies.

**3.8. Chorion Villus Sampling (CVS):** It will be performed when the diagnosis is made at early gestational ages for the performance of QF-PCR, array-CGH and DNA reserve for panel/exome.

**3.9. Neurosonography:** Not included in the initial study, but recommended in cases of early hydrops that have been reversed, to rule out lesions caused by the hydrops state, or in cases without diagnosis to try to find alterations that can guide us to the cause.

**3.10. Study of the neonate:** Importance of the multidisciplinary study (pediatrics, genetics, etc.) of a live newborn with hydrops when a prenatal etiological diagnosis has not been reached.

**3.11. Post-mortem studies:** In cases of fetal or neonatal death and legal termination of pregnancy, it is very important to perform a **necropsy and placental biopsy**, which will help us to clarify the etiology in up to 80-85% of cases according to series described. Without these tests we cannot conclude the study of NIH. In some selected cases, an **MRI** will be considered as a complementary imaging test.

## 4. CLINICAL MANAGEMENT AND OBSTETRIC ATTITUDE

Counseling of a couple with a diagnosis of NIH will depend on the etiologic diagnosis, the possibility of intrauterine treatment and the gestational age. It is important to try to complete the etiological study in idiopathic hydrops because of the influence that it can have on future pregnancies. **Necropsy** is often a key test to close the diagnosis and should always be offered.

If the hydrops is diagnosed at a viable gestational age and is susceptible to treatment or if an expectant attitude is decided, **fetal well-being** must be monitored according to protocol and with serial ultrasounds for fetal morphologic and hemodynamic control.

**4.1. Fetal therapy in NIH:**

- **Intrauterine transfusion in anemia:** Acquired maternal red cell aplasia, fetomaternal hemorrhage, fetal hemolysis due to G6PD deficiency, fetal parvovirus B19 infection, anemia of unknown origin.
- **Aspiration of cavities or shunt:** pleural effusion, ascites, pulmonary cysts, Congenital Cystic Adenomatoid Malformation (CCAM)/sequestration complex, pulmonary lymphangiectasia.

- **Intravascular or maternal treatment of fetal arrhythmia:** Tachyarrhythmia, AV block (anti-Ro/La).
- **Treatment of maternal and fetal infection in syphilis, toxoplasma and CMV.** Specific protocol "TORCH Infections".
- **Fetal surgery:** CCAM/sequestration complex, sacrococcygeal teratoma, complications of monochorionic gestation, critical aortic or pulmonary stenosis.

**4.2. Maternal complications. Mirror syndrome or Ballantyne's syndrome:** It is a potentially serious and rare **maternal complication** associated with hydrops, presenting proteinuria, hypoproteinemia, edema, water retention, arterial hypertension, oliguria, dilutional anemia, thrombocytopenia, elevated uric acid, liver enzymes and creatinine. Acute pulmonary edema has been described in up to 20% of cases. The analytical findings are compatible with preeclampsia and it has been called mirror syndrome since edema appears in both the mother and the hydropic fetus. Treatment consists of diuretics, antihypertensive drugs and intensive monitoring with water balance and rest. The definitive treatment will be the resolution of the fetal hydrops and if this is not possible, the termination or gestation.

**4.3. Obstetric complications:** If associated with polyhydramnios, complications inherent to this situation may appear such as PROM, placental abruption and preterm delivery.

**4.4. The route of delivery** will be decided according to obstetric reasons and taking into account the probable prognosis. In viable fetuses, urgent transfer to a level III center for monitoring and delivery assistance is important. If pleural effusion is present, thoracentesis for intrauterine lung re-expansion should be performed immediately before birth. In cases of poor prognosis or non-viable fetuses, thoracentesis or paracentesis may be performed to facilitate a vaginal delivery if there is a risk of dystocia.

**4.5 Counseling:** The prognosis of non-immune fetal hydrops will depend on the underlying cause and gestational age at diagnosis, as well as the possibility of prenatal treatment.

- **High overall mortality** (50-70%) depending on etiology (higher in fetuses with GA < 24 weeks, chromosomal and structural anomalies).
- **Neonatal morbidity** depends on etiology. Better outcomes in treatable causes but insufficient long-term follow-up studies. Reported risk of neurodevelopmental delay around 10%.

- **Prenatal etiologic diagnosis** is possible in 50-60% of cases.
- **Etiological diagnosis (pre- and postnatal)** is possible in 75-80% of cases.
- The **risk of recurrence** will depend on the etiology and the underlying diseases and therefore it is sometimes difficult to assess if we do not find the cause.

  The probability of recurrence of an idiopathic NIH is rare, but NIH caused by metabolic and/or genetic disorders can have up to a 25% recurrence rate and it is therefore very important to accurate the diagnosis with the tests currently available (blood test, array-CGH, exome/gene panel of Hydrops-RASopathies and Noonan syndrome, viral PCR, necropsy, placental biopsy, MRI, etc.) to make a good prenatal assessment.

**TABLE 1. SUMMARY TABLE OF NON-IMMUNE HYDROPS STUDY**

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|---|---|
| **CLINICAL HISTORY** | Ethnicity (alpha-thalassemia)<br>Familiar history (metabolopathies, congenital anomalies)<br>Personal history (diabetes, previous hydrops, perinatal deaths, jaundice in previous child, history of infections, history of exanthema, travel, contact with children, STD risk behaviors, consanguinity |
| **MATERNAL BLOOD TEST** | Full blood count and coagulation<br>Blood group and Rh and irregular antibodies<br>Biochemistry (liver function tests, uric acid)<br>Serology: IgG and IgM for: parvovirus B19, CMV, syphilis (regain tests (VDRL or RPR) and treponemal tests), toxoplasma, rubella (absence of previous immunity), Zika in epidemiological risk history, Kleinauer-Betke test (fetomaternal hemorrhage).<br>In selected cases<br>• Glucose tolerance test (suspicion of poorly controlled DBT)<br>• Hemoglobin electrophoresis (assess according to ethnicity and history<br>• G6PD and pyruvate kinase<br>• Anti-Ro and anti-La antibodies (fetal bradyarrhythmia)<br>• Prenatal karyotype/array |
| **FETAL STUDY** | |
| **ULTRASOUND** | Anatomy: Rule out structural malformations and markers of infection<br>Amniotic fluid index and placental thickness<br>Biophysical profile. Fetal movements<br>Doppler study: |

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|---|---|
| | • Systolic peak MCL(>1.5 MoM predictive value or severe anemia)<br>• Arterial and venous Doppler to assess fetal hemodynamic status |
| **ECHOCARDIOGRAPHY** | Structural and functional |
| **AMNIOCENTESIS**<br>(20-25 mL) | QF-PCR and array-CGh<br>PCR-DNA infection study (parvovirus B19, CMV, herpes simplex, enterovirus, treponema pallidum, arenavirus, toxoplasma and Zika If epidemiological history or risk).<br>DNA reserve for exome/gene panel<br>Biochemical study of metabolopathies |
| **CORDOCENTESIS**<br>(nonheparinazed EDTA tubes) | QF-PCR and Array-CGH if necessary (1 mL)<br>Full blood count (FBC)<br>Blood group<br>Direct Coombs test<br>Liver functional tests } 2 mL<br>Optionally:<br>• Study of specific metabolopathies<br>• Directed exome/gene panel (hydrops-RASopathies and Noonan)<br>• Hemoglobin study |
| **FETAL EFFUSION STUDY (pleural effusion or ascites)** | Lymphocyte count (pleural effusion)<br>Protein/albumin ratio<br>Creatinine/ionogram (ascites)<br>Possibility of genetic studies |
| **CHORIONIC VILLUS SAMPLING** | QF-PCR, array-CGH and DNA pool for gene/exome panel targeting hydrops-RASopathies and Noonan in early gestational age |
| **NEUROSONOGRAPHY** | Second-line study in non-diagnosed cases and to rule out lesions in cases of early hydrops resolved |
| **NEONATAL STUDY** | Multidisciplinary study (pediatrics, genetics, etc.) in cases without diagnosis. |
| **POSTMORTEM STUDY** | Fetal necropsy: investigate dysmorphic syndrome or skeletal dysplasia with skeletal examination<br>X-Ray and possible MRI<br>Study the placenta (macro and microscopically): tumors, signs of infection, metabolopathies<br>Reserve fetal blood if feasible, and also tissues, DNA and supernatant amniotic fluid for subsequent biochemical, genetic or infectious studies |