Fetal and Neonatal Hydrops

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Contents

Abstract

Hydrops fetalis (i.e., fetal hydrops) (HF) is a serious condition defined as abnormal accumulation of fluid in two or more fetal compartments. It presents as ascites, pleural effusion, pericardial effusion, and skin edema. In some patients, it may also be associated with polyhydramnios and placental edema. Potter was the first to distinguish nonimmune hydrops fetalis (NIHF) from immune hydrops. These days approximately 90% of cases of hydrops fetalis are due to nonimmune diseases. The basic mechanism for the formation of HF is an imbalance between interstitial fluid production and lymphatic return. The antenatal diagnosis of HF is made by the ultrasound finding of fluid accumulation in the fetus or placenta. The management of hydrops fetalis is a great challenge for fetal medicine specialists and neonatologists and the mortality rate still remains high.

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95.1 Salient Points

- Hydrops fetalis is a serious condition defined as abnormal accumulation of fluid in two or more fetal compartments.

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- Approximately 90% of cases of hydrops fetalis are due to nonimmune diseases.
- The basic mechanism for the formation of hydrops fetalis is an imbalance between interstitial fluid production and lymphatic return.
- Main causes of hydrops fetalis are: hematological disorders, cardiovascular and infectious conditions, genetic abnormalities, tumors, and idiopathic origins.
- The management of hydrops fetalis is still a great challenge for fetal medicine specialists and neonatologists and the mortality caused by this pathology varies widely.
- The hydropic fetus is usually in a precarious state and even minimal delay in the diagnosis may hamper access to life-saving procedures.

95.2 Introduction

Hydrops fetalis (i.e., fetal hydrops) (HF) is a serious condition defined as abnormal accumulation of fluid in two or more fetal compartments. It presents as ascites, pleural effusion, pericardial effusion, and skin edema (Fig. 1). In some patients, it may also be associated with polyhydramnios and placental edema. Potter was the first to distinguish nonimmune hydrops fetalis (NIHF) from immune hydrops (Potter 1943).

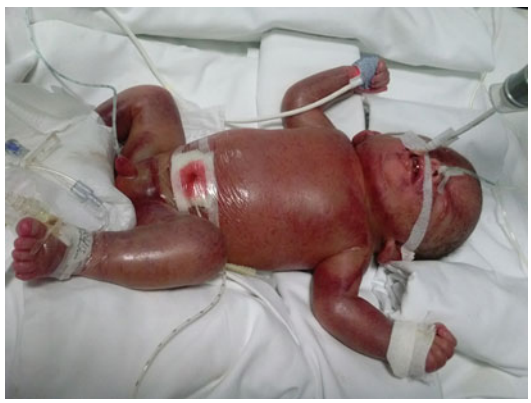

Fig. 1 Preterm newborn with NIHF

95.3 Epidemiology

In the past, hemolytic disease due to Rh incompatibility used to be the main cause of both fetal and neonatal immune hydrops. These days approximately 90% of cases of hydrops fetalis are due to nonimmune diseases, with the number of affected live born ranging from 1:1500 to 1:3800 (Santolaya et al. 1992; Warsof 1986). Hydrops fetalis is much more common in Southeast Asia; in Thailand the expected frequency of nonimmune hydrops fetalis due to homozygous alpha-thalassemia or Bart hydrops ranges from one every 500 to one every 1500 pregnancies (Suwanrath-Kengpol et al. 2005; Abrams et al. 2007). Although the availability of ultrasound technology has greatly improved antenatal diagnosis of HF, perinatal mortality (PNM) remains high.

95.4 Pathogenesis

The basic mechanism for the formation of HF is an imbalance between interstitial fluid production and lymphatic return. Fluid accumulation in the fetus can be due to (a) heart failure, (b) anemia, (c) obstructed lymphatic flow, or (d) decreased plasma osmotic pressure. The fetus is particularly susceptible to interstitial fluid accumulation because of its greater capillary permeability, compliant interstitial compartments, and predisposition to increased venous pressure because of impaired lymphatic return (Abrams et al. 2007; Apkon 1995). Clinical and animal studies have shown that high central venous pressure (CVP) has a pivotal role in the development of fetal hydrops (Shinbane et al. 1997). Increased CVP causes edema and effusions by increasing capillary hydrostatic pressure and decreasing lymphatic return (Moise et al. 1992). Albumin is the main oncotically active plasma protein and when its hepatic synthesis is impaired transcapillary fluid movement increases (Abrams et al. 2007; Apkon 1995). Hypoproteinemia and hypoalbuminemia are common in human hydrops; however, studies in humans and animals have shown that hypoalbuminemia is unlikely to trigger this condition (Pasman et al. 2006).

95.5 Etiology

Regardless of the known causes of immune hydrops, extensive pre- and postnatal investigations have improved our knowledge of the etiology of nonimmune hydrops fetalis (NIHF). Indeed, larger series and a systematic review report that a cause can be found in nearly 60% of cases prenatally (Santo et al. 2011) and in 85% when postnatal detection is included (Bellini et al. 2009). HF is an end-stage process and a nonspecific finding associated with a range of abnormalities. Its causes can be divided into six broad categories: hematological disorders, cardiovascular and infectious conditions, genetic abnormalities, tumors, and idiopathic origins. Table 1 summarizes the causes of fetal hydrops.

95.6 Diagnosis

A pregnant woman with polydramnios, severe anemia, toxemia, or isoimmune disease should undergo further investigation. The antenatal diagnosis of HF is made by the ultrasound finding of fluid accumulation in the fetus or placenta. Specifically, excess serous fluid should be identified in at least one space (ascites, pleural effusion, or pericardial effusion), accompanied by skin edema (>5 mm thick), or fluid in two potential spaces without edema (Mahony et al. 1984; Romero et al. 1988). Ascites can be detected when a minimum of 50 mL is present in the fetal abdomen (Holzgreve et al. 1984). Polyhydramnios and placental thickening (typically defined as a placental thickness ≥4 cm in the second trimester or >6 cm in the third trimester (Lee et al. 2012; Hoddick et al. 1985)) may be present, but oligohydramnios is a particularly ominous finding when it develops in nonimmune hydrops fetalis (Fleischer et al. 1981). It is important to perform middle cerebral artery Doppler studies to assess the presence of fetal anemia. The fetus with NIHF due to severe anemia will have increased velocity through the middle cerebral artery (Mari et al. 2000).

Women with NIHF may develop the mirror syndrome, also referred to as Ballantyne's syndrome. In this uncommon complication the mother presents with an edema that "mirrors" that of her hydropic fetus. The mirror syndrome may represent a form of preeclampsia and is characterized by edema in approximately 90% of cases, hypertension in 60%, and proteinuria in 40% (Braun et al. 2010).

The subsequent workup of the hydropic fetus should focus on detecting the underlying cause. In general, the first step is to collect detailed information on the mother's medical history, specifically in relation to hereditary or metabolic diseases, diabetes, anemia, exposure to infectious agents, and use of medication. The second step includes a detailed ultrasound examination of the fetus and an accurate workup of the mother. The third step, after obtaining the results on the mother's conditions, is a systematic approach to the fetus, including invasive testing, such as villocentesis, amniocentesis, cordocentesis, and sampling of any effusions. Invasive investigations of the fetus are necessary when maternal blood and ultrasound examination fail to provide a definitive cause of HF. The recommended workup of a fetus with HF is shown in Table 2.

If the etiology of HF is not identified before birth, postnatal investigations should be carried out. Blood samples for laboratory analysis are similar to those taken antenatally: blood group including Rh status, direct Coombs antibody screen, full blood cell count, karyotype, metabolic and chemistry studies, hemoglobin electrophoresis, if indicated. Structural defects should be evaluated using skeletal radiographs and ultrasound. A genetic consultation may also be helpful, particularly to determine the risk of recurrence. In case of intrauterine or neonatal death, an autopsy is mandatory.

95.7 Treatment

The management of hydrops fetalis is a great challenge for fetal medicine specialists and neonatologists. The hydropic fetus is usually in a precarious state, and even minimal delays could hamper access to life-saving procedures (Désilets et al. 2013).

Table 1 Causes of hydrops fetalis

Hematological	Genetic
Isoimmunization (immune hydrops) (hemolytic disease of the newborn, erythroblastosis) Rh (most commonly D; also C, c, E, e) Kell ABO Others Other hemolytic disorders Glucose phosphate isomerase deficiency Pyruvate kinase deficiency G-6-PD deficiency Disorders of red cell production Diamond-Blackfan syndrome Leukemia (usually associated with Down or Noonan syndrome) Alpha-thalassemia (Bart hemoglobinopathy) Parvovirus B19 Others Fetal hemorrhage Placental subchorial tumors Fetomaternal hemorrhage Twin-to-twin transfusion Isoimmune fetal thrombocytopenia Others	Inborn errors of metabolism Glycogen-storage disease, type IV Lysosomal storage diseases Hypothyroidism and hyperthyroidism Others Genetic syndromes Chromosomal syndromes Beckwith-Wiedemann syndrome (trisomy 11p15) Cri-du-chat syndrome (chromosomes 4 and 5) Trisomy 10, mosaic Trisomy 13 Trisomy 15 Trisomy 18 Trisomy 21 (Down syndrome) Turner syndrome (45, X) Others
Cardiovascular	**Tumors and others**
Structural anomalies Abnormalities of left ventricular outflow Abnormalities of right ventricular outflow Other vascular malformations Nonstructural anomalies Obstruction of venous return Supraventricular tachycardia Congenital heart block Prenatal closure of the foramen ovale or ductus arteriosus Myocarditis Idiopathic arterial calcification or hypercalcemia	Intrathoracic tumors or masses Abdominal tumors or masses Other conditions Placental choriocarcinoma Placental chorangioma Cystic hygroma Intussusception Meconium peritonitis Intracranial teratoma Sacrococcygeal teratoma
Infectious	**Idiopathic**
Parvovirus B19 Cytomegalovirus (CMV) Syphilis Herpes simplex Toxoplasmosis Hepatitis B Adenovirus Ureaplasma urealyticum Coxsackievirus type B Listeria monocytogenes	

A woman with a hydropic fetus should be hospitalized in a level-3 perinatal centre if antenatal nonstress testing (NST) (American Pregnancy Association 2006) and biophysical profile (BPP) (Manning 1999) are not reassuring (Table 3). At the same time, efforts should be continued to determine the underlying etiology of HF. Delivery is indicated after 34 weeks' gestation, or earlier if there is evidence of a mature fetal lung profile at amniocentesis or if the fetal condition deteriorates. Delivery is also necessary in the presence of obstetric indications or compromised maternal conditions due to the mirror syndrome (maternal hydrops) (Van Selm et al. 1991; Norton et al. 2015).

Table 2 Antenatal evaluation of hydrops fetalis

Maternal history
Age, parity, gestation
Hereditary or metabolic diseases, anemia
Recent infections or contacts
Medication use
Maternal laboratory evaluation
Complete blood cell count
Blood type, Rh, indirect Coombs antibody screen
Kleihauer-Betke stain
Syphilis, TORCH, and parvovirus B19 titres
Culture for group B streptococcus, Listeria
Maternal triple screen
Oral glucose tolerance test
Optional, as indicated:
Metabolic studies
Hemoglobin electrophoresis
G6PD, pyruvate kinase
Autoimmune screen (SLE, anti-Ro and -La)
Ultrasonography
Identify anatomic abnormalities
Evaluate extent of edema and effusions
Rule out twin gestation
Doppler blood flow assessment
Fetal echocardiography
Evaluate for cardiac malformation, arrhythmia
Amniocentesis
Karyotype
Culture or PCR for TORCH, parvovirus
Amniotic fluid a-fetoprotein
Restriction endonucleases (thalassemias)
Lecithin-sphingomyelin ratio, phosphatidyl glycerol to evaluate lung maturity
Fetal blood sampling
Karyotype
Complete blood cell count
Blood type; hemoglobin electrophoresis
Blood chemistries, albumin, gases
Culture or PCR for TORCH, parvovirus
Metabolic testing (Tay-Sacks, Gaucher, GM_1 gangliosidosis)
Fetal effusion sampling
Culture or PCR for TORCH, parvovirus
Protein content
Cell count and cytology

G6PD glucose-6-phosphate dehydrogenase, *PCR* polymerase chain reaction, *SLE* systemic lupus erythematosus, *TORCH* toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex

Modified from Swain et al.: Prenatal diagnosis and management of nonimmune hydrops fetalis. Aust N Z J Obstet Gynaecol 39:285, 1999

Table 3 Conservative management in hospital

Hospitalize the patient in case of
Fetal skin thickening
Pericardial effusion
Nonreactive NST
Biophysical profile (BPP) ≤ 6
Subjective decreased fetal movement
Gestational age below 32–34 weeks
Treat underlying cause, if possible
Administer antenatal corticosteroids
Monitor serial growth and effusion volumes
NST and BPP every 2 or 3 days

NST nonstress test

The appropriate treatment of the fetus with hydrops, which carries a high mortality risk, can only be undertaken after a precise and detailed diagnosis. Full parental involvement is essential, because the associated abnormalities may be severely debilitating or even lethal. In addition, invasive fetal treatment and elective preterm delivery remain controversial. Therefore, obstetricians, fetal medicine specialists, and neonatologists should consult themselves on the optimal timing of delivery, also involving pediatric surgeons, cardiologists, and cardiothoracic surgeons. Various anecdotal approaches are found in the literature, but no properly designed clinical trials have been performed to provide the clinician with evidence-based management. Furthermore, the hydropic process may resolve spontaneously. Thus, the available management schemes aim to correct the underlying pathophysiology, including fetal transfusion to correct anemia (regardless of the cause), drug treatments for cardiac arrhythmias, correction or reduction of space-occupying lesions that impede cardiac venous or lymphatic return, and procedures intended to stop fetal blood loss (regardless of the cause) (Watson and Campbell 1986; Muller-Hansen et al. 1998; Jones 1995).

Fetal transfusion with packed red blood cells (RBCs) given intraperitoneally has become accepted as standard care for fetuses with severe anemia. It carries low risk, despite the lack of definitive evidence from randomized clinical trials. This approach has been used successfully in

the treatment of severely anemic fetuses of isoimmunized pregnancies and to correct anemia due to various other causes – unless the pregnancy is at an advanced gestational age and the risks associated with delivery are considered to be less than those associated with the procedure (Norton et al. 2015). Alternative routes (percutaneous umbilical vein, intrahepatic umbilical vein, umbilical artery, intracardiac transfusions) for the administration of blood products to the fetus have been reported. Other approaches are aimed at the mother, fetus, and newborn baby. Maternal plasmapheresis, promethazine, or corticosteroids have been used for the mother. Fetal therapies available include partial packed-cell exchange transfusion, fetal intravenous IgG, platelet transfusion, and the administration of human granulocyte-stimulating factor. Neonatal stem cell transplantation has been used for α-thalassemia (Carr et al. 1995). However, these newer therapeutic techniques carry greater risk for the fetus than the intraperitoneal route and should therefore be used cautiously.

Highly vascularized tumor masses and acute, massive twin-to-twin hemorrhages are life-threatening diseases that may justify life-threatening treatment. Techniques such as tumor debulking surgery, surgery for active bleeding, photocoagulation, and radiofrequency thermal ablation may all be helpful in the treatment of fetal conditions such as sacrococcygeal tumors, highly vascularized fetal intraabdominal, thoracic, or placental masses, and when there is massive arteriovenous shunting (Bullard and Harrison 1995; Rubod et al. 2006).

The management of the twin-to-twin transfusion syndrome is currently an unresolved problem: treating an anemic fetus with transfusions has shown no evidence of benefit; volume reduction for the transfusion recipient or a combination of transfusion and fetal reduction has rarely been used or may not correct the ongoing pathophysiology. Furthermore, feticide of the affected twin is often followed by the development of hydrops in the previously normal surviving twin (Mahone et al. 1993).

Treatments of fetal arrhythmias include taking no action, pharmacological treatment, and immediate delivery. Maternal treatment with antiarrhythmic medications for NIHF secondary to fetal tachyarrhythmia is recommended, unless the gestational age is close to term or there is a maternal or obstetrical contraindication. On the other hand, in-utero therapy for fetal bradyarrhythmia resulting in hydrops is considered investigational and is not generally recommended outside of a research setting (Norton et al. 2015).

In the presence of fetal maturity, the simplest and most direct approach is delivery of the affected fetus and treatment of the arrhythmia directly after birth. Possible treatment options include digitalis, furosemide, flecainide, verapamil, amiodarone, propanolol, procainamide, quinidine, adenosine, sotalol, terbutaline, corticosteroids, and immunoglobulins. Various drug combinations are also used. However, the choice of the drug remains empirical and arbitrary, until definitive evidence from clinical trials becomes available (Strasburger et al. 1986; Simpson and Sharland 1998).

The management of space-occupying masses varies depending on the type of lesion and from center to center. If immediate delivery is not practicable, the mass is either reduced or removed. Pleural and pericardial effusions and ascites may be treated with single or serial drainage. Fetal surgery with definitive correction of the underlying anomaly has also been used. Successes and failures have been reported with all methods; there is no evidence suggesting that one approach is better than another (Wesolowski and Piazza 2008).

Postnatal management of HF poses a unique set of problems for the neonatologist. Treatment of the infant after delivery is facilitated by the knowledge of the underlying cause. In addition to appropriate equipment and supplies for resuscitation, a skilled team of health care professionals (neonatologists, nurses, respiratory therapists, and radiology and ultrasonography technicians) should be present in the delivery room (McMahan and Donovan 1995; American Heart Association 2006). Fluid in the pleural, pericardial, and abdominal cavities may require aspiration in the delivery room to allow adequate ventilation and circulation. Umbilical arterial and venous catheters are sited to monitor and treat arterial pressure, blood gases, venous pressure, hematocrit, and the metabolic

state of the infant. Packed red cells or whole blood cross matched with the mother should be available for the correction of severe anemia by partial exchange transfusion, even if this is due to non-immune causes. Surfactant therapy and mechanical ventilation are used to manage surfactant deficiency and pulmonary hypoplasia, which may be associated with hydrops. Fluid intake is based on an estimate of the infant's "dry weight" (e.g., 50th percentile for gestational age) and kept to a minimum (e.g., 40–60 mL/kg/day) until the edema is resolved. Inotropic support (e.g., dopamine) may be required to improve cardiac output (Mascaretti et al. 2003; Teixeira et al. 2008).

In case of death, it is mandatory to continue the investigation postmortem of the fetus or newborn with NIHF. Genetic counseling, clinical photography, and fetal X-rays should be obtained to evaluate possible dysmorphic syndrome or skeletal dysplasia. Autopsy is strongly recommended. Additional procedures include storage of fetal blood, tissue, DNA, and amniotic fluid supernatant. Placental examination (microscopy, histopathology) focusing on tumors, fetal anemia, infection, and metabolic disorder is indicated (Désilets et al. 2013).

95.8 Prognosis

Estimates of mortality vary widely. The condition has a mortality rate of virtually 100% when structural defects are present or the cause of HF is unknown. Most case series report 60–90% mortality, although notable improvements have been described (Abrams et al. 2007). The prognosis of NIHF due to cardiac structural abnormalities is poor, with combined fetal and infant mortality reported as 92%, largely due to the severity of the heart defects causing in utero congestive heart failure (Randenberg 2010). Treatable causes of hydrops, such as fetal arrhythmia or infection with parvovirus B19, have a better prognosis (Bonvicini et al. 2011). However, when the congenital infection (parvovirus) occurs in the early second trimester (<20 weeks of gestation) the risk of a poor outcome for the fetus is greatest (Lamont et al. 2011).

In cases of tachyarrhythmias, the prognosis has been improved by antenatal antiarrhythmic treatment. Cases presenting before 24 weeks' gestation have a worse prognosis, whereas those that present later may benefit from delivery and intensive neonatal care (McCoy et al. 1995).

Although idiopathic NIHF has a low recurrence risk, the risk for some cases of NIHF may be as high as 25%, making genetic counseling an integral part of the management of any patient with NIHF (Norton et al. 2015).

Czernik et al. reported that, among liveborn infants, neonatal mortality with NIHF is as high as 60%. Temporal trends suggest that the associated mortality has not improved over the past two decades. In addition to the small sample size, an explanation for the lack of improvement in survival over time may be that the more severe cases are now more frequently diagnosed prenatally and referred to tertiary centers (Czernik et al. 2011).

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