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Clinical and virological aspects of human parvovirus B19 Infection during Gestation.

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Chapter 2

Aetiology, Diagnosis and Treatment of Hydrops Foetalis



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Abstract

Hydrops foetalis is defined as a state of excessive fluid accumulation in the extra vascular compartment of the foetus, leading to widespread soft tissue oedema and/or accumulation of fluid in the foetal body cavities. The prognosis of hydrops foetalis is highly dependent on the underlying pathology and early diagnosis is essential to identify treatable cases. The classification of immune and non-immune hydrops foetalis describes the difference between Rhesus haemolytic disease of the newborn and other aetiologies leading to hydrops foetalis. With improved diagnosis and treatment of Rhesus iso-immunisation, non-immune factors have become more frequent. Distinction between anaemic and non-anaemic hydrops foetalis provides a far more useful differentiation between aetiologies. This approach is used to discuss differential diagnosis, work-up and therapeutic options in hydrops foetalis. A structured multidisciplinary work-up will facilitate early diagnosis and assist in making treatment decisions.

Introduction

Hydrops foetalis is a clinical condition in which excessive fluid accumulation in the extra vascular compartment of the foetus leads to widespread soft tissue oedema and/or the collection of fluid in the foetal body cavities. The mortality rate is high and depends on the underlying aetiology and gestational age at the time of occurrence. The first sign of foetal hydrops in early pregnancy (11-15 weeks of gestation) is often the presence of generalized skin oedema in the foetal head and neck area at ultrasound investigation. Pleural effusions are rarely diagnosed before 15 weeks of gestation.

Hydrops foetalis can be divided into Immune Hydrops Foetalis (IHF, 12.7% of cases), associated with antigen-antibody mediated red cell haemolysis, and Non-Immune Hydrops Foetalis (NIHF, 87.3% of cases), associated with a wide range of aetiological factors (1, 2). With improved treatment and diagnosis of Rhesus iso-immunisation, non-immune factors have become more frequent causes of hydrops foetalis. The incidence of NIHF is estimated at 1 in 3000 pregnancies (3). In NIHF 63% of cases can be divided into five main causes: cardiovascular, chromosomal, thoracic, twin-twin transfusion syndrome (TTTS), and anaemia (3). Infectious and metabolic diseases can also cause NIHF (1, 4-7). NIHF has a favourable outcome in 27.5% of cases (2), with idiopathic NIHF carrying the worst prognosis. Negative prognostic factors described are enlarged biventricular dimension, early manifestation of pericardial effusion (8, 9), and pulmonary hypoplasia secondary to pleural effusions (1, 9, 10). Pleural fluid drainage in utero may improve outcome in NIHF (10, 11) and timely performed thoraco-amniotic shunting procedures are associated with a 60% survival rate (11-14).

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Classification of hydrops foetalis

The current classification of immune and nonimmune hydrops foetalis is not sufficient to describe the complex pathophysiology leading to heart failure and generalized oedema in the foetus and neonate and is confusing since immunological phenomena play a role in both entities. A more practical approach to describe the aetiology of hydrops foetalis is based on the presence or absence of anaemia. The distinction between anaemic and non-anaemic hydrops foetalis (AHF and NAHF) allows for a more structured approach towards diagnosis and therapy.

Anaemic Hydrops Foetalis (AHF): aetiology (Table 1).

AHF has two main groups of causative factors: haematological disorders and intrauterine infections

Haematological disorders

Hydrops foetalis is caused by haematological disorders in 10-27% of the cases (1, 15). Haematological disorders include G6PD deficiency, pyruvate kinase deficiency, aplastic anaemia, congenital leukaemia (as in trisomy 21 (16)) and congenital dyserythropoietic anaemia (15). Foetal anaemia by alpha-thalassaemia is a major cause of AHF in South-East Asia (12, 15). Hereditary spherocytosis (an autosomal dominant erythrocyte membrane defect resulting in potassium efflux) may lead to anaemic hydrops foetalis at 25 weeks of gestation (17). The most common type of AHF (62.5%) is Rhesus (RhD, Rhc) allo immunisation. Other, less frequent, causes of AHF are Kell antigen- (12.5%), Fy-antigen, and ABO-allo immunisation. No differences in survival have been reported between hydropic foetuses with Rh (D)- and Kell-immunisation (18). Intrauterine transfusion in immune anaemic hydrops foetalis dramatically improves foetal and neonatal outcome and reverses hydrops foetalis in 65%. A younger gestational age at first transfusion and the number of successful transfusions are positively correlated with survival (18). When intrauterine transfusion is delayed and severe hydrops develops, survival rates decline from 92% to 55%.

Table 1. Anaemic Hydrops Foetalis (AHF): differential diagnosis.

Aetiology	Description	Diagnosis
G6PD deficiency	X-linked, female carriers. Mediterranean patients. Role in hexose monophosphate shunt. Haemolysis due to oxidant shock, drugs, fava beans, infections.	Enzyme assay, reticulocytosis, blister cells & Heinz bodies in blood film.
Pyruvate kinase deficiency	Most common defect after G6PD def. Autosomal recessive. Homozygote has haemolysis. Reduced production of ATP → rigid erythrocytes.	Anaemia, prickle (distorted)-cells, reticulocytosis, pyruvate kinase activity < 20%.
Hereditary spherocytosis	Autosomal dominant inheritance. Red cell membrane defect, rigid & less deformable erythrocytes → haemolysis.	Anaemia, spherocytes and reticulocytes in blood film, increased osmotic fragility, direct Coombs test is negative.
Alpha-thalassaemia	Deletion of one or both alpha-genes on each chromosome 16 → ↓ alpha chain synthesis → dysbalance globin chain → precipitation → haemolysis.	Anaemia, microcytosis, reticulocytosis, Hb-electrophoresis, globin-chain synthesis studies.
Aplastic anaemia	Congenital = rare, aplasia of bone marrow, immune mediated, acquired (drug mediated).	Pancytopenia, no reticulocytes.
Cong leukaemia	All originating from B-cell stemcell. Higher frequency of AML. Poor prognosis. Associated with Down's and Noonan syndrome. Differentiate from transient myeloproliferative disorder in Down's syndrome.	Blood film, blasts, leukocytosis. Bone marrow aspirate.

ABO-alloimmunisation Kell/-Duffy/-Fy ^a - immunisation	Sensitisation during delivery, transplacental bleeding, amniocentesis, chorion villus sampling, miscarriage.	Maternal serum testing for antibodies (IgG), rise in titre? Direct Coombs reaction cord blood.
Rhesus-immunisation	Ibid.	Blood group typing, Rhesus type.
Foeto-maternal haemorrhage	Transplacental bleeding.	Kleihauer test.
Congenital infections - Parvovirus B19 - Cong syphilis	Congenital infections leading to foetal anaemia.	Cord sampling: Spec IgM/IgG antibodies, PCR. FTA-ABS test, TPHA, VDRL.

Intrauterine infections

Intrauterine foetal infections associated with the development of AHF are parvovirus B19, toxoplasmosis, adenovirus, coxsackie virus, rubella, cytomegalovirus, leptospirosis and congenital hepatitis, and syphilis (1, 19). Symptoms include anaemia, hepatic dysfunction, hypoproteinemia, and portal hypertension. Hydrops secondary to syphilis carries a grave prognosis. Serological tests in the affected hydropic foetus may be negative due to the prozone phenomenon, i.e. a false negative test because overwhelming antibody titres interfere with proper antigen-antibody complex formation necessary to visualise a positive test result (1, 19). This problem can be resolved by diluting the affected serum to as much as 1:1,024 or greater, which should always be done in high-risk situations with foetal hydrops of unknown aetiology.

The main body of research has been directed towards parvovirus B19 infection in pregnancy. Parvovirus B19, a small "parvo" single stranded DNA virus, accounts for 27% of cases of AHF in anatomically normal foetuses (6). The viral genome codes for three proteins of known function: NS1 (replicative functions and cellular cytotoxicity), VP1 (role in developing immunity against parvo B19 virus and in viral entry into cells), and VP2 (role in developing immunity and arthropathy by inducing cross reactive antibodies).

Maternal infection with parvo B19 virus occurs in 0.25-6% of susceptible pregnancies (6). In a cohort of 2279 pregnant women screened for anti-parvovirus B19-IgG and IgM-antibodies, 114 pregnant women showed an acute parvovirus infection, 32% in the first, 54% in the second, and 14% in the third trimester (20). The relative risk of maternal parvovirus B19 infection was 2.8% if the source was a related child living in the household (6). If the mother has positive IgG titres for parvovirus at the time of exposure, the risk of transmission to the foetus is minimal. IgG antibodies are directed to either one or both of the two capsid proteins VP1 and VP2. VP1 is required for an effective immune response. A positive maternal IgM titre for parvovirus is indicative for infection with a high risk of transmission to the foetus. Maternal viraemia reaches its peak approximately 1 week after infection and symptoms such as erythema infectiosum, mild fever, arthralgia, and headache start approximately 17 days after infection. Immediately following maternal viraemia the foetus can be infected. The parvovirus B19 receptor, abundant in the placenta in early gestation,

may provide a pathway to the foetus (6, 21). Viral infection of the foetus may persist until term or after birth, even when infection occurs in early gestation. The interval between parvo B19 infection and development of AHF ranges from 2 to 6 weeks (22). Some case reports even mention development of AHF twenty weeks after infection with Parvovirus B19 (21). Seventy percent of all cases of AHF associated with parvo B19 infection occur between 20 and 24 weeks of gestation (11). When infection occurs before 20 weeks an association with early foetal loss has been described.

Parvo B19 virus is diagnosed by detection of viral DNA by PCR on cordocentesis blood samples and/or amniotic fluid or identification of specific IgM-antibodies (6). Virus culture usually fails. Foetuses infected with parvovirus B19 develop severe thrombocytopenia and anaemia with a pronounced erythroblastic reaction, hepatitis, excessive hepatic iron deposits, and early development of hydrops foetalis. The foetus is particularly susceptible during the early hepatic stage of erythropoiesis. In this stage, the half-life of red blood cells is shorter compared to the later bone marrow/splenic haematopoietic phases (22, 23). The abundance of the parvo B19 virus cellular receptor globoside (the blood group P antigen) on red blood cells explains its tropism for erythroid cells (6, 22). The NS1 protein of parvovirus B19 is associated with viral replication, target cell cytotoxicity, viral activation and possibly with apoptosis mediated death of red blood cells (23). Specific IgG antibodies against the NS1 protein are linked with more severe or chronic parvo B19 virus infections (24). The P antigen is also present on foetal myocardial cells, consistent with the observations of parvovirus B19 myocarditis in foetuses (25). Parvovirus B19 myocarditis complicates anaemia induced congestive heart failure in utero.

Intrauterine transfusion of red blood cells and/or platelets increases foetal survival from 55 to 82% (6). Resolution of hydrops foetalis following successful intrauterine transfusion may take up to 12 weeks (26). Successful intrauterine transfusion for parvo B19 virus induced foetal anaemia and correction of AHF results in a good neurodevelopment prognosis (27). Negative prognostic factors are maternal seroconversion during early gestation, low gestational age at detection of AHF, number and results of intrauterine transfusion, and prolonged duration from intrauterine transfusion to resolution of hydrops foetalis. Overall foetal mortality of parvovirus B19 infection is estimated to be 9% (6). There are a few reports suggesting an association of foetal malformation with parvo B19 infection but causality seems unlikely. A recombinant immunoglobulin is being developed for the prevention of parvoviral infections in the future. Seronegative women or women with known hemoglobinopathies could be inoculated with this vaccine to prevent parvovirus infection during pregnancy.

Anaemic Hydrops Foetalis (AHF): prenatal diagnosis by ultrasound

Doppler investigations by ultrasound play an important role in the diagnosis of foetal anaemia (28, 29). Blood flow in anaemic foetuses has a hyper dynamic pattern, which can be detected with Doppler velocimetry in various foetal blood vessels. Velocity changes are

thought to result from increased cardiac output and decreased viscosity of foetal blood. Blood flow in the middle cerebral artery (MCA) is the first to respond to foetal anaemia due to the early response of the brain tissue to anaemia. The MCA peak systolic velocity (PSV) may identify anaemic fetuses (29-32). Sensitivities from 64 to 100% have been reported (28, 29). A MCA-PSV > 1 SD has a sensitivity of 64% and specificity of 100% to identify cases with haematocrit levels > 2 SD below the mean value for gestational age (31). Cosmi et al. (30) reported a 94.1% sensitivity in detecting foetal anaemia caused by parvo B19 virus using MCA-PSV measurements. Doppler flow of the MCA is superior to liver and spleen measurement in detecting foetal anaemia (33). When rapid haemolysis occurs, without time to adapt, increased MCA velocity may be detected before the development of spleen or liver enlargement.

The correlation between MCA velocity changes and anaemia becomes more accurate as the anaemia worsens (29). Doppler ultrasonography has the advantage of being non-invasive, which can be used to predict the presence of foetal anaemia and identify patients before using more invasive diagnostic methods such as cordocentesis. Cordocentesis should be reserved for cases where foetal anaemia is suspected and intrauterine transfusion is likely to follow. MCA-PSV is also useful in determining the success of intrauterine transfusion. The correction of foetal anaemia by intrauterine transfusion significantly decreases the foetal MCA-PSV (34). Therapy-resistant foetal hydrops may be due to massive injury of foetal vascular endothelium (18, 35). Long-term free iron overload, due to repeated intrauterine transfusions and free radical damage of endothelial cells may also be a mechanism for therapy resistant AHF (18, 36). However, a recent study suggests that repeated red blood cell transfusions do not pose a significant risk factor for oxidative stress in utero (37).

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Non-Anaemic Hydrops Foetalis (NAHF)

NAHF has many causes, including genetic abnormalities, inborn errors of metabolism, TTTS, congenital heart defects, foetal supraventricular tachycardia, intrathoracic pathology, endocrine pathology, and intestinal ischemia leading to meconium peritonitis.

Genetic abnormalities

Chromosomal abnormalities are the most common cause of NAFH before 24 weeks of gestation (5, 11) and are reported in 10% of all hydrops foetalis cases (1). A study by Jau-niaux and colleagues concerning 898 cases of hydrops foetalis (600 NAFH cases after 1982 compared with 298 cases before 1982) describes the most frequently identified genetic abnormalities. Genetic causes of hydrops foetalis were chromosomal disorders in 15.7%, alpha-thalassaemia in 10.3%, skeletal dysplasia in 4%, arthrogyrosis multiplex syndromes in 1.8%, multiple pterygium syndrome in 1.5% and lysosomal storage disease in 1.0% (16). Turner's syndrome is associated with incomplete formation of the lymphatic system draining into the thoracic duct, leading to hydrops foetalis. Trisomy 21, 18, and 13 (5, 16, 38) and

Smith-Lemly-Opitz syndrome (39) are also associated with NAHF (5, 16, 38). Other syndromes associated with hydrops foetalis (osteogenesis imperfecta (4%) and Neu-Laxova syndrome (1, 16). These genetic syndromes have been associated with NAHF, but the precise mechanism of development of NAHF is unknown in these cases. Cardiac defects, often associated with genetic syndromes, may also contribute to NAHF. Genetic metabolic diseases causing hydrops foetalis are lysosomal diseases (1.0%) (40). These diseases are autosomal recessively inherited and are discussed in the next paragraph. The list of genetic abnormalities described in association with NAHF is elaborate. Some of the most frequent causes are listed below in Table 2.

Table 2. Non-Anaemic Hydrops Foetalis (NAHF): genetic abnormalities.

Syndrome	Main signs	Diagnosis
Turner	Small stature, broad chest, webbed neck, ovarian dysgenesis, anomalous auricles, cong. Lymph oedema, cardiac (valve) defect. Mean IQ: 90.	Xo, 45 chromosomes.
Arthrogryposis multiplex	Joint contractures, secondary deformities. Clubfoot, dislocated hips. Normal bones. Degeneration (or non development) of muscular tissue.	Non-progressive muscular disorder, unknown aetiology.
Osteogenesis imperfecta	Failure to thrive, abnormal dentition, thin and translucent skin, postnatal onset limb deformity, fractures, scoliosis, kyphosis, impaired hearing. Macrocephaly, triangular facial appearance. Abnormal bone tissue with reduced osteoblasts, disorganised osteoid, sparse trabeculae.	Autosomal dominant, variability in expression. Defect in production of collagen type I.
Neu-Laxova	Prenatal growth deficiency. Microcephaly, lissencephaly, absent corpus callosum; cerebellum or olfactory bulbs. Micrognathia, protruding eyes, short neck, scaling skin, oedema, ichthyosis, short limbs, syndactyly. Cataract, microphthalmia.	Autosomal recessive.
Trisomy 21	Hypotonia, open mouth, protruding tongue, mental deficiency. Brachycephaly, low nasal bridge, inner epicanthic folds. Strabismus, cataracts, myopia. Small ears, hearing loss. Short neck, single crease hands, wide gap first-second toe. Cardiac defect. Primary gonadal deficiency.	Trisomy 21 (full: 94%, mosaicism: 2.4%)
Trisomy 18	Feeble foetal activity, premature birth, polyhydramnions, IUGR. Mental deficiency. Micrognathia, low set ears, narrow palatal arch. Clenched hand. Umbilical hernia, diastasis recti. Cardiac defect, genital abnormality.	Trisomy 18, mosaicism and partial trisomy exist.
Trisomy 13	Holoprosencephaly, seizures, severe mental defect. Microcephaly, wide sagittal suture. Cleft palate, low set ears. Deafness. Haemangioma, cardiac abnormality, abnormal genitalia, camptodactily, polydactily.	Trisomy 13, mosaicism exists.

Inborn errors of metabolism

Lysosomes are present in all nucleated cells and are involved in the degradation of macromolecules. Lysosomal enzymes remove terminal residues from these molecules, the resulting monomeric units are transported out of the lysosomes. Approximately 75 lysosomal

enzymes are involved in these processes. Defects in these enzymes give rise to specific lysosomal storage diseases (40, 41).

Inborn errors of metabolism lead to NAHF through obstruction of the venous bloodstream by visceromegaly and local circulatory problems secondary to storage substances (particularly in the reticuloendothelial system). Generalised oedema and extreme hepatosplenomegaly can be seen in lysosomal disorders. Anaemia may result from hypersplenism and reduction of erythropoietic stem cells by bone marrow infiltration with storage cells (40). Hypoproteinemia due to liver dysfunction may cause hydrops. Cardiomyopathy due to lysosomal storage disease is rare in the neonatal period, but glycogen storage disease type II (Pompe disease) and mucopolysaccharidosis may present in this way (42). Clinical investigation of the hydropic neonate is essential since dysmorphisms such as a “Hurler-like” phenotype or hepatosplenomegaly may point to the diagnosis. In lysosomal storage disease, the placenta is pale and bulky and microscopy shows the presence of lysosomal vacuolation.

Lysosomal storage disorders associated with NAHF are summarized in Table 3. Especially cases of familial NAHF should be investigated for lysosomal storage disorders as parental consanguinity is a known risk factor. The diagnosis can be established by investigating specific metabolites in cultured cells (fibroblasts, amniotic fluid cell or chorionic villous tissue), amniotic fluid or urine. Most lysosomal storage disorders are autosomal recessively inherited, so definite diagnosis is of great importance (39, 41-43).

Table 3. Non-Anaemic Hydrops Foetalis (NAHF): lysosomal storage disorders [40].

Disease	Biochemical defect
Mucopolysaccharidosis IV	Galactose-6-sulfatase deficiency
Mucopolysaccharidosis VII Sly	Beta-glucuronidase deficiency
Sialidosis II(congenital form)	Neuraminidase deficiency
Galactosialidosis	Cathepsin A, beta-galactosidase and neuraminidase deficiency
Nieman-Pick disease type C	Cellular trafficking of exogenous cholesterol
Gaucher disease type II	Acid beta-glucosidase deficiency
GM 1 gangliosidosis	Beta galactosidase deficiency
Mucopolysaccharidosis I Hurler	Alpha-L-iduronidase deficiency
Mucopolyliposis II I-cell disease	Phosphotransferase deficiency
Dissiminated lipogranulomatosis, Farber	Ceramidase deficiency

Cardiac causes

Cardiac causes of NAHF include structural heart disease, foetal tachyarrhythmia, cardiomyopathy, and myocarditis (Table 4).

Structural heart disease

Structural heart disease has been reported in 13.8 to 40% all NAHF cases (1, 43). After 24 weeks of gestation, congenital heart disease is the most common cause of hydrops foetalis (5, 11). Congestive heart failure is the primary cause in these cases of NAHF and can be due to major anatomical cardiac anomalies such as a large atrio-ventricular septal defect (16% of NAHF cases), hypoplastic left or right heart condition, and critical aortic stenosis (44). In a study of NAHF by Allan and colleagues (45) structural heart disease occurred in 62% and tachyarrhythmia in 38%. Foetal echocardiography is a useful tool for diagnosis and monitoring progress of disease.

Foetal tachyarrhythmia

Sustained foetal supraventricular tachycardia is rare, but frequently leads to NAHF. Naheed and colleagues described 30 patients with prenatal diagnosed supraventricular tachycardia, 73% had 1:1 atrioventricular conduction and 27% had a block (46). NAHF due to Wolff-Parkinson-White syndrome or tachyarrhythmia due to atrial flutter can be successfully treated with anti-arrhythmic medication (5, 47, and 48). Maternally administered Digoxin is the first-line treatment option to resolve foetal hydrops due to cardiac arrhythmia, Flecainide is often used as an alternative therapy for foetal supraventricular tachycardia causing NAHF (49, 50). Placental oedema and poor placental function can impair transplacental delivery of drugs. In those cases direct intraperitoneal or intravascular foetal therapy is a good alternative and more direct option (47). The combination of transplacental Amiodarone and Digoxin therapy has been used with success (47), though Amiodarone may cause foetal hypothyroidism and intrauterine growth retardation. Sotalol is another effective treatment of foetal tachycardia with excellent placental transfer (51). After conversion to a normal sinus rhythm, total resolution of hydrops requires 4-6 weeks (48). If conversion to normal heart rhythm is delayed beyond 1 week, heart failure is likely to progress and hydrops will worsen (47). The risk of recurrence of prenatal diagnosed (and treated) arrhythmias is 48%, in particular when severe prenatal hydrops is present or if Wolff-Parkinson-White syndrome is diagnosed (52).

Cardiomyopathy

Cardiomyopathy comprises 8-11% of all cardiovascular problems diagnosed in utero (43). Intrinsic causes of foetal cardiomyopathy are Noonan syndrome, familial dilating cardiomyopathy (DCM), lysosomal disease and maternal type I (insulin dependant) diabetes. The most common form of DCM is that seen in infants born of diabetic mothers (42, 53). This form of cardiomyopathy will completely resolve in 6-12 months. It is caused by deposition of fat and glycogen in the myocardium. Foetal DCM is also associated with maternal autoimmune disease, such as SLE, and the presence of anti-Ro or anti-La antibodies. This DCM is often accompanied by atrio-ventricular conduction pathology. Outcome is extremely poor with foetal death occurring in 80% (42). Diastolic dysfunction in cardiomyopathy is associated with the highest risk of mortality (42).

Myocarditis

Foetal myocarditis may be caused by infectious agents or by autoimmune diseases. Infectious causes of foetal myocarditis include coxsackie B-, adeno- and parvo B19 virus infections (54). The development NAHF is promoted by congestive heart failure and/or arrhythmia. The course of the illness is frequently fulminant or fatal.

Table 4. Non-Anaemic Hydrops Foetalis (NAHF): cardiac causes (42, 45, 46, 51, 54).

Defect	Description
Structural heart defect	Left ventricular outflow abnormalities: <ul style="list-style-type: none"> • Aortic valvular stenosis • Aortic valvular atresia • Coarctation of the aorta • Truncus arteriosus • Hypoplastic left heart Right ventricular outflow abnormalities: <ul style="list-style-type: none"> • Pulmonary valve stenosis/atresia • Ebstein anomaly • AV-malformation • Placental haemangioma • Umbilical cord haemangioma • Hepatic haemangioma
Obstruction of venous return	<ul style="list-style-type: none"> • Superior/inferior v cava obstruction • Umbilical cord torsion/varix • Intrathoracic/-intra abdominal tumour
Tachyarrhythmia	<ul style="list-style-type: none"> • Supraventricular tachycardia • Congenital heart block (in maternal collagen disease)
Cardiomyopathy	<ul style="list-style-type: none"> • Noonan syndrome • Familial dilating cardiomyopathy • Lysosomal disease • Maternal type I diabetes
Myocarditis	<ul style="list-style-type: none"> • Parvovirus B19, coxsackie-B virus, adenovirus

Intrathoracic causes

Intrathoracic abnormalities associated with NAHF (Table 5) are pleural effusions (primary or secondary), congenital cystic adenomatoid malformation of the lung (CCAM) (55), pulmonary sequestration (a non-aerated mass of pulmonary tissue supplied by a systemic artery), mediastinal teratoma, and bronchogenic cysts. Right-sided congenital diaphragmatic hernia (CDH) with herniated liver tissue may also lead to NAHF (56). Familial pulmonary lymphatic hypoplasia is an autosomal recessive inherited disease with pleural effusions and NAHF in the second half of gestation due to hypoplasia of the distal intralobular and terminal bronchiolar lymphatic system (57). Non specific foetal pleural effusion,

one of the features (or causes) of hydrops foetalis, can be either unilateral or bilateral. It is found in 1:15,000 pregnancies and is associated with lung tumours, goitre, viral infections (adenovirus, cytomegalovirus and parvo B19 virus), and trisomy 21. The pathophysiology of hydropic changes in primary pleural effusion is probably vena cava obstruction and cardiac obstruction resulting in low output cardiac failure (57). Congenital chylothorax is another cause of NAHF with an incidence of 1:10,000-15,000 pregnancies (male: female ratio = 2:1). Perinatal mortality is 98% when associated with NAHF, which is probably due to loss of protein with chyle into the pleural space leading to hypoalbuminaemia and generalised oedema. Serial thoracentesis or thoraco-amniotic shunt placement improves survival. The earliest prenatal pleural drainage procedure described was performed at 17 weeks gestational age (58). Postnatal treatment consists of thoracentesis, replacement of intravascular volume and protein, and prolonged parenteral nutrition or medium chain triglyceride feeding (59).

Table 5. Non-Anaemic Hydrops Foetalis (NAHF): intrathoracic causes.

Primary pulmonary pathology	<ul style="list-style-type: none"> • congenital cystic adenomatoid malformation • pulmonary sequestration • bronchogenic cysts
Intrathoracic tumours	<ul style="list-style-type: none"> • mediastinal teratoma
(Other) space occupying lesion	<ul style="list-style-type: none"> • diaphragmatic hernia
Pleural effusions	<ul style="list-style-type: none"> • non specific • infectious • malignant • chylothorax

Twin-twin transfusion syndrome

Twin-twin transfusion syndrome (TTTS), which complicates monochorionic twin gestation in 15% of cases, can be a cause of NAHF [60]. TTTS presents during the second trimester with an oligo-polyhydramnion sequence, i.e. the deepest vertical pool in the donor sac is <2 cm and in the recipient's sac >8 cm. Staging has been described by Quintero et al. (61, 62):

- Stage I: bladder in donor visible
- Stage II: bladder in donor not visible
- Stage III: pathologic umbilical artery or recipient reverse flow in ductus venosus or abnormal Doppler readings in the donor (absent/reduced end-diastolic flow, pulsatile umbilical venous flow)
- Stage IV: hydrops foetalis
- Stage V: demise of one or both twins

TTTS is associated with high morbidity and mortality and may develop rapidly over days. Acute severe TTS occurs in 1%. TTTS is caused by an unbalanced interfetal transfusion via vascular anastomoses in monochorionic twins. It is mediated by mostly > 1 arteriole-venous

anastomoses in association with absent bi-directional superficial anastomoses. Superficial arterio-arterial anastomoses seem to play a protective role. There is a nine fold reduction in likelihood of developing TTTS when these arterio-arterial anastomoses are present (60). Fetal hemodynamics is disturbed by an increased expression of vasopressors such as endothelin, renin, and angiotensin II and a decrease in vasodilators such as nitric oxide (NO). Hypertension and raised levels of endothelin-1 have been described in recipient foetuses. The risk of congenital heart disease is increased up to 12-fold in TTTS, mainly due to pulmonary valve stenosis in recipient twins. The recipient twin can develop signs of fluid overload and high output cardiac failure, including cardiomegaly, ascites and pleural-pericardial effusions (hydrops foetalis). Hydropic changes may be seen in the recipient, donor, or both. Hydrops foetalis has been described as early as 14 weeks of gestation (63). When hydropic changes occur in the second trimester, prognosis is extremely poor. Antenatal demise of the recipient twin in TTTS can be associated with subsequent development of hydrops foetalis in the surviving twin donor. This phenomenon may be due to ischemia-reperfusion injury of the previously poorly perfused twin (64). Hydropic signs in the donor foetus may also be seen after selective laser coagulation procedures (25% of cases), they are transient and caused by an increase in foetal circulating volume and adaptation after occlusion of vascular anastomoses (65). This phenomenon has also been reported after amnioreduction procedures (66). In general, these hydropic changes are not associated with a poor prognosis. However, foetal monitoring for hydropic signs is necessary after laser- and amnioreduction procedures since foetal hydrops may persist and complicate delivery and neonatal resuscitation.

Treatment modalities for foetal hydrops in TTTS include serial amnioreduction (to reduce the risk of preterm labour by reducing increased amniotic pressure, overall survival: 60%; double survival: 50%; single survival 20%), septostomy (creating a hole in the intertwin membrane, overall survival: 83%), and laser ablation of vascular anastomoses (overall survival of cases presenting < 28 weeks: 58%, double survival: 42%; single survival: 32%). In severe stage III/IV disease, selective feticide by bipolar diathermy of the umbilical cord has been performed to rescue one child (60, 67). Treatment can be based on the Quintero staging system: stage I/II: serial amnioreduction, stage III: selective laser ablation, severe stage III/IV: selective feticide.

Long-term sequelae of TTTS consist of psychomotor retardation and cerebral palsy. Both donor and recipient are at risk. Lopriore et al. (68) report a 21% incidence of cerebral palsy and abnormal neurodevelopmental outcome in TTTS survivors, who were at least 4 years of age at follow up. Adverse neurological outcome was associated with intrauterine foetal death of a co-twin (due to acute exsanguination of the surviving twin into the diseased or moribund twin through existing vascular anastomoses). This may lead to cerebral white matter damage in the surviving twin. Laser ablation therapy is associated with a lesser (4-9%) risk of cerebral palsy than serial amnioreduction (29%).

Gastrointestinal aetiology: meconium peritonitis

Gastrointestinal diseases associated with development of NAHF (Table 6) are tracheo-oesophageal fistula, small bowel volvulus, bowel duplication and meconium peritonitis. Meconium peritonitis is a sterile chemical peritonitis induced by meconium leaking into the peritoneal cavity following perforation of the bowel (most commonly the ileum) proximal to a site of obstruction. Obstruction is caused by atresia, stenosis, volvulus, intussusception, meconium ileus (cystic fibrosis is present in 7.7-40% of cases), imperforate anus and peritoneal bands (69). The perforation has closed by the time of birth, but the resulting adhesions between bowel loops and omentum wall up the meconium collection forming pseudo cysts which can be detected by prenatal ultrasound. Mostly pseudo cysts are seen in association with foetal ascites and polyhydramnion (69, 70). Meconium peritonitis is rare before 20 weeks gestation (69). In a study by Zerbini et al. (24) parvo B19 virus infection was associated with stenosis in jejunum and ileum leading to perforation and subsequent meconium peritonitis. It is speculated that vascular inflammation can lead to bowel ischemia and bowel perforation (71). Meconium peritonitis due to bowel perforation has also been associated with acute maternal hepatitis A and B infection, but the underlying pathophysiology is unknown (72). In the presence of meconium peritonitis and hydrops, an intrauterine parvo B19, hepatitis A or B virus infection should be excluded besides anatomical abnormalities of the bowel.

Table 6. Non-Anaemic Hydrops Foetalis (NAHF): meconium peritonitis.

Infectious causes Vascular inflammation → bowel ischemia	Parvovirus B19 Congenital Hepatitis A infection Congenital Hepatitis B infection
Anatomical	Tracheo-oesophageal fistula Small bowel volvulus Bowel duplication Bowel atresia
Obstructive → perforation proximal to obstruction site	Meconium ileus (Cystic Fibrosis) Peritoneal bands Intussusception Atresia

Endocrine aetiology

Several case reports suggest a possible relationship between foetal hypothyroidism and pleural effusions. Thyroid hormone may play a role in the regulation of lymphatic flow rate and lung liquid clearance since a case of foetal chylothorax resulting in NAHF resolved after treatment with thyroxin (73). NAHF secondary to foetal tachycardia has been reported in foetal hyperthyroidism due to thyroid-stimulating immunoglobulins in maternal Graves disease and could be treated by administration of anti-thyroid drugs to the mother (74).

Conclusions

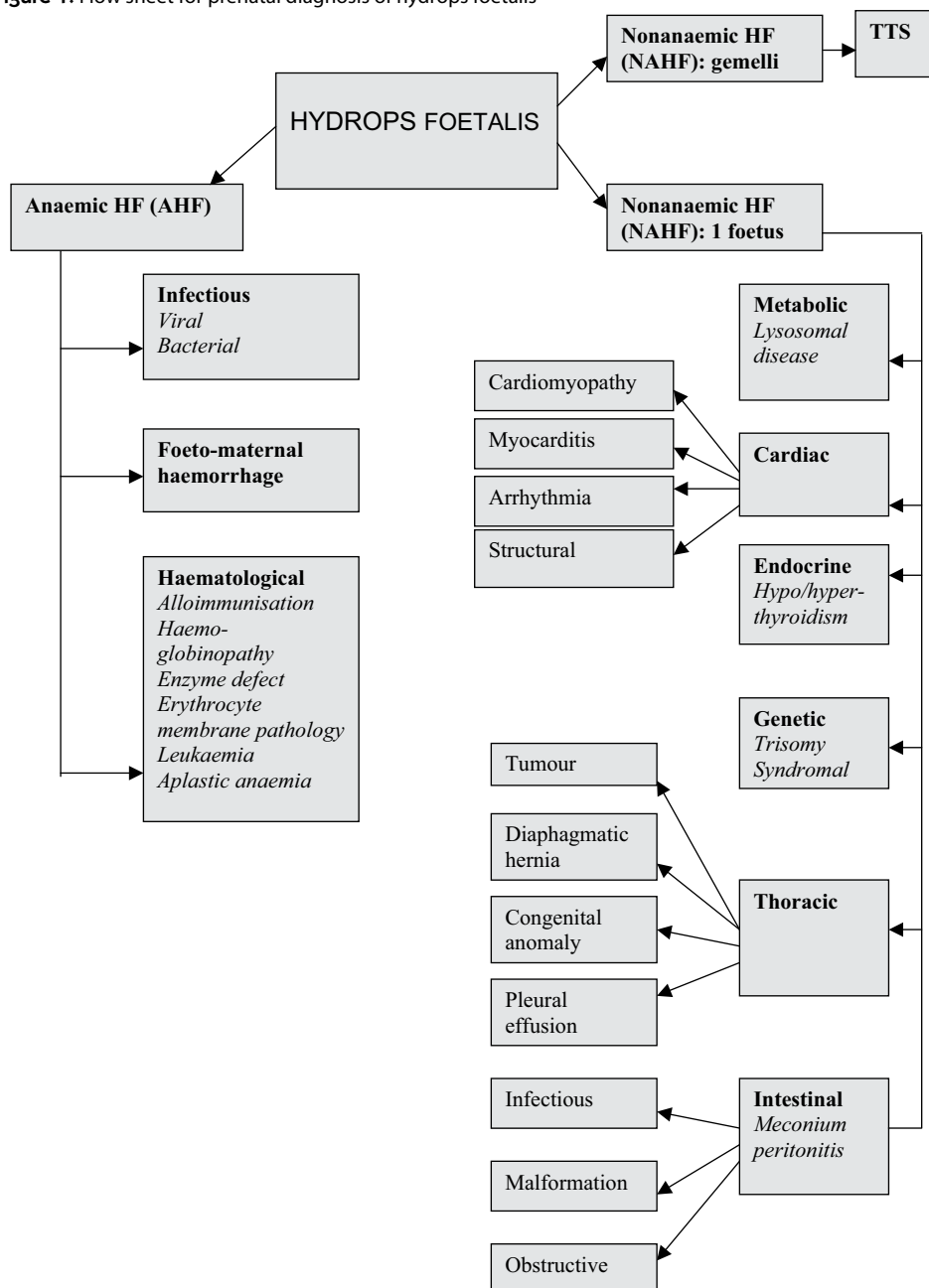
Hydrops foetalis is a state of excessive fluid accumulation in the extra vascular compartment of the foetus leading to widespread soft tissue oedema and/or the collection of fluid in the foetal body cavities. A distinction should be made between Anaemic Hydrops Foetalis (AHF) and Non-Anaemic Hydrops Foetalis (NAHF).

Aetiology of anaemic hydrops foetalis consists of hemoglobinopathies, Rhesus or ABO allo immunisation syndromes and viral infections such as parvovirus B19 infection. Hydrops foetalis often resolves after correction of foetal anaemia with intrauterine transfusions with a good postnatal neurodevelopmental outcome. Foetal ultrasound is a highly sensitive, non-invasive tool to estimate the degree of foetal anaemia and evaluate the effect of intrauterine transfusions. Middle cerebral artery peak systolic flow is the measurement of choice. Cordocentesis provides access for direct foetal therapy and diagnostic purposes (blood group and Rhesus typing, serology and PCR for congenital infections, and chromosomal studies).

Non-anaemic hydrops foetalis is caused by multiple pathologies. Genetic abnormalities (10% of all NAHF cases) are the most common cause of hydrops foetalis before 24 weeks of gestation. Inborn errors of metabolism such as lysosomal storage disease constitute 1% of NAHF cases. Diagnosis can be made on amniotic fluid, fibroblasts or chorionic villous tissue and most of these diseases are autosomal recessively inherited. Early diagnosis is of major importance in counselling parents and making treatment decisions. Cardiac aetiologies comprise structural defects, reduced contractility and arrhythmias. Congenital heart defects (14-40% of cases of NAHF) lead to congestive heart failure in utero. Structural heart disease should always be looked for during foetal ultrasound in hydrops foetalis. Foetal tachycardia (mainly re-entry tachycardia) causes hydrops foetalis when sustained (>12 hrs). Maternally administered medications as Digoxin, Flecainide, Amiodarone or Sotalol are used to convert to normal sinus rhythm in utero. Following administration of these drugs resolution of hydrops foetalis may take 4-6 weeks. Cardiomyopathy (11% of cardiovascular diagnoses in utero) should be looked for in NAHF. Infectious aetiologies leading to NAHF may play a part in the development of foetal myocarditis. Intrathoracic and intra-abdominal anomalies of the foetus may lead to hydrops foetalis. Intrathoracic causes of NAHF are congenital (pulmonary) tumours, mediastinal hernia, congenital malformation of lymphatic drainage (leading to pleural fluid accumulation) and infectious pleural effusions. Diagnosis can mostly be made by ultrasound. When diagnosis is made early, drainage of pleural effusions is advocated to prevent pulmonary hypoplasia. Intra-abdominal malformations and congenital viral infections (such as parvovirus B19, CMV or hepatitis A & B infections) may cause intestinal hypoxemia leading to bowel necrosis and perforation. Intrauterine bowel perforation due to meconium ileus should always be part of the differential diagnosis. Prognosis depends on the underlying pathology. Endocrine causes of NAHF are rare and include hypo- and hyperthyroidism.

Due to the elaborate list of possible aetiologies leading to hydrops foetalis, a structured approach as reflected by the flow sheet in Figure 1 is advocated. Hydrops foetalis is a challenging entity for both the obstetrician and the neonatologist. Early diagnosis and treatment greatly improves perinatal outcome.

Figure 1. Flow sheet for prenatal diagnosis of hydrops foetalis



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