

Investigation and Management of Non-immune Fetal Hydrops

This clinical practice guideline has been prepared by the Genetics Committee, reviewed by Maternal Fetal Medicine Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Valérie Désilets, MD, Montreal QC

François Audibert, MD, Montreal QC

GENETICS COMMITTEE

R. Wilson, MD (Chair), Calgary AB

François Audibert, MD, Montreal QC

Jo-Ann Brock, MD, Halifax NS

June Carroll, MD, Toronto ON

Lola Cartier, MSc, Montreal QC

Alain Gagnon, MD, Vancouver BC

Jo-Ann Johnson, MD, Calgary AB

Sylvie Langlois, MD, Vancouver BC

William MacDonald, MD, Halifax NS

Lynn Murphy-Kaulbeck, MD, Moncton NB

Nanette Okun, MD, Toronto ON

Melanie Pastuck, RN, Cochrane AB

Vyta Senikas, MD, Ottawa ON

Disclosure statements have been received from all contributors.

Key Words: Non-immune hydrops fetalis, fetal hydrops, fetal therapy, fetal metabolism

J Obstet Gynaecol Can 2013;35(10):e1–e14

Abstract

Objective: To describe the current investigation and management of non-immune fetal hydrops, with a focus on treatable or recurring etiologies.

Outcomes: To provide better counselling and management in cases of prenatally diagnosed non-immune hydrops.

Evidence: Published literature was retrieved through searches of PubMed or MEDLINE, CINAHL, and The Cochrane Library in 2011 using key words (non-immune hydrops fetalis, fetal hydrops, fetal therapy, fetal metabolism). Results were restricted to systematic reviews, randomized controlled trials/controlled clinical trials, observational studies, and significant case reports. Additional publications were identified from the bibliographies of these articles. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to May 2012. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Benefits, harms, and costs: These guidelines educate readers about the causes of non-immune fetal hydrops and its prenatal counselling and management. It also provides a standardized approach to non-immune fetal hydrops, emphasizing the search for prenatally treatable conditions and recurrent genetic etiologies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Recommendations

1. All patients with fetal hydrops should be referred promptly to a tertiary care centre for evaluation. Some conditions amenable to prenatal treatment represent a therapeutic emergency after 18 weeks. (II-2A)
2. Fetal chromosome analysis and genetic microarray molecular testing should be offered where available in all cases of non-immune fetal hydrops. (II-2A)
3. Imaging studies should include comprehensive obstetrical ultrasound (including arterial and venous fetal Doppler) and fetal echocardiography. (II-2A)

This document reflects emerging clinical and scientific advances on the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁷⁸

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.⁷⁸

- Investigation for maternal–fetal infections, and alpha-thalassemia in women at risk because of their ethnicity, should be performed in all cases of unexplained fetal hydrops (II-2A).
- To evaluate the risk of fetal anemia, Doppler measurement of the middle cerebral artery peak systolic velocity should be performed in all hydropic fetuses after 16 weeks of gestation. In case of suspected fetal anemia, fetal blood sampling and intrauterine transfusion should be offered rapidly. (II-2A)
- All cases of unexplained fetal hydrops should be referred to a medical genetics service where available. Detailed postnatal evaluation by a medical geneticist should be performed on all cases of newborns with unexplained non-immune hydrops. (II-2A)
- Autopsy should be recommended in all cases of fetal or neonatal death or pregnancy termination. (II-2A) Amniotic fluid and/or fetal cells should be stored for future genetic testing. (II-2B)

Epub ahead of print.
This document will be published in:
J Obstet Gynaecol Can 2013;35(10)

ABBREVIATIONS

- AF amniotic fluid
- CBC complete blood count
- CMV cytomegalovirus
- FISH fluorescent in situ hybridization
- Hb hemoglobin
- HbH hemoglobin H
- MCA middle cerebral artery
- MPS mucopolysaccharidosis
- NICHD National Institute of Child Health and Human Development
- NIHF non-immune hydrops fetalis
- QF-PCR quantitative fluorescent polymerase chain reaction
- RT-PCR real-time polymerase chain reaction
- TORCH toxoplasmosis, rubella, cytomegalovirus, herpes simplex
- UA umbilical artery
- VZV Varicella-zoster virus

INTRODUCTION

Hydrops fetalis is defined as the accumulation of abnormal fluid in at least two different fetal compartments. It implies an excess of total body water, which is usually evident as extracellular accumulation of fluid in tissues and serous cavities.^{1,2} It generally presents as subcutaneous edema, accompanied by effusions in two or more serous cavities including pericardial or pleural effusions, and ascites. Polyhydramnios or placental thickening (> 6 cm) are often associated. When the fluid accumulation is limited to one cavity, for example isolated ascitis or pleural effusion, the situation should be described in terms of the involved site, since this may be helpful in narrowing the differential diagnosis. The three primary mechanisms associated with hydrops are intrauterine anemia, intrauterine heart failure, and hypoproteinemia. In addition to these three basic mechanisms, fetal hydrops

has a causal relationship with a variety of structural abnormalities that interfere with the fetoplacental circulation. Chromosomal anomalies (aneuploidy, deletion, duplication, genetic mutation) and skeletal dysplasia may also be associated with hydrops through a variety of mechanisms.^{1,2}

Fetal hydrops carries a poor prognosis; however, several etiologies can be treated in utero with potential good results. The growing number of recognized etiologies requires a comprehensive and systematic search for causes, in particular for treatable or recurrent conditions.

Recommendation

1. All patients with fetal hydrops should be referred promptly to a tertiary care centre for evaluation. Some conditions amenable to prenatal treatment represent a therapeutic emergency after 18 weeks. (II-2A)

DEFINITIONS

Immune versus Non-Immune Fetal Hydrops

Immune hydrops

Maternal red cell alloimmunization occurs when a pregnant woman has an immunological response to a paternally-derived antigen that is foreign to the mother and inherited by the fetus.³ The maternal antibodies may cross the placenta, bind to antigens present on the fetal erythrocytes, and cause hemolysis, hydrops fetalis, and fetal death. The prognosis of this condition has been considerably improved over the last decades, due to interventions including antenatal and postpartum Rhesus immune globulin, non-invasive prenatal surveillance with cerebral Doppler, and intrauterine transfusion. The complete description and management of this condition is beyond the scope of this guideline.^{3,4}

Non-immune hydrops

Non-immune hydrops fetalis refers to hydrops in the absence of maternal circulating red-cell antibodies.⁵ With the introduction of widespread immunoprophylaxis for red cell alloimmunization and the use of in utero transfusions for immune hydrops therapy, non-immune causes have become responsible for at least 85% of all cases of fetal hydrops.⁶ The reported incidence is around 3 per 10 000 births; however, the incidence is much higher at the first- and second-trimester ultrasounds because of higher fetal death rates.⁷

Hydrops in the First Trimester and Cystic Hygroma

Signs of hydrops can be found as early as in the first trimester. This is usually seen in association with increased nuchal translucency and/or cystic hygroma,^{8,9} a septated

cystic structure in the occipitocervical region and sometimes the axillary region. The evaluation of increased nuchal translucency and cystic hygromas with or without fetal hydrops differs from that of non-immune fetal hydrops and is beyond the scope of this guideline. Pertinent SOGC guidelines can be found elsewhere.¹⁰⁻¹²

Twin Gestation as a Different Situation

Non-immune fetal hydrops in one or both twins may imply a different etiology, especially in monochorionic twins, given the possibility of twin-to-twin transfusion syndrome. Review articles discussing the assessment and management of twin-to-twin transfusion syndrome and other complications specific to twin pregnancies are available elsewhere.¹³⁻¹⁷

ETIOLOGIES

Despite extensive investigations, the etiology of non-immune fetal hydrops may remain unknown in 15% to 25% of patients.^{1,6,18-20} The goal of this guideline is to propose a standardized approach to the investigation and management of non-immune fetal hydrops with a focus on the rare treatable or potentially recurring causes. A growing number of conditions can result in NIHF. A systematic review has recently analyzed a total of 225 relevant articles describing 5437 individual cases of NIHF.²¹ All cases were sub-classified into one of the following diagnostic categories: cardiovascular (21.7%), hematologic (10.4%), chromosomal (13.4%), syndromic (4.4%), lymphatic dysplasia (5.7%), inborn errors of metabolism (1.1%), infections (6.7%), thoracic (6.0%), urinary tract malformations (2.3%), extra-thoracic tumours (0.7%), twin-to-twin transfusion or placental (5.6%), gastrointestinal (0.5%), miscellaneous (3.7%), and idiopathic (17.8%). See Table 2 for details.

Chromosomal Abnormalities

Chromosomal abnormalities are the cause of NIHF in 25% to 70% of cases.²² The risk of fetal aneuploidy is higher when identified earlier in gestation or when fetal structural anomalies are seen.^{5,23} Standard fetal chromosome analysis is indicated in all cases of hydrops. Additional genetic microarray molecular testing should be considered in all NIHF cases as the NICHD Microarray Study has shown additional genetic chromosomal anomalies (smaller than can be seen by standard cytogenetic studies) in 7% of fetuses with congenital anomalies and standard normal karyotype.²⁴

Recommendation

2. Fetal chromosome analysis and genetic microarray molecular testing should be offered where available in all cases of non-immune fetal hydrops where available. (II-2A)

Table 2. Conditions associated with non-immune fetal hydrops

Cases, n	Cardiovascular	Hematologic	Chromosomal	Infection	Thoracic	Syndromic	Placental (TTTS)	Lymphatic dysplasia	Idiopathic	Various*
	1181	564	727	366	327	237	304	310	966	455
%	21.7	10.4	13.4	6.7	6.0	4.4	5.6	5.7	17.8	8.4
Potential fetal therapy	Yes† (anti-arrhythmic drugs)	Yes (IUT)	No	Yes (IUT for parvovirus)	Yes (Thoraco-amniotic shunting)	No	Yes (Placental laser therapy)	No	No	No

Adapted from Bellini et al.^{19,26}

Based on a total number of 5437 cases of NIHF

IUT: intrauterine transfusion; TTTS: twin-to-twin transfusion syndrome

*including: inborn storage diseases, urinary tract malformations, extra-thoracic tumours, gastro-intestinal, miscellaneous

†For fetal tachyarrhythmias only

Cardiac Etiologies

Cardiac etiologies account for 10% to 20% of cases of NIHF.^{2,25} These include not only structural abnormalities, but also cardiac arrhythmias, tumours, physiological dysfunction due to infection, inflammation, infarction, and arterial calcification. Cardiac and intrathoracic lesions that result in right atrial pressure or volume overload seem to be most commonly associated with hydrops fetalis. Fetal cardiac tumours, cardiomyopathy, and other myocardial conditions probably result in hydrops fetalis by a similar mechanism. Fetal tachyarrhythmia has been shown to result in elevation of atrial pressure and is the most treatable of cardiac causes of hydrops fetalis.²⁶ Fetal bradyarrhythmias are less easily treatable and a rare causative mechanism of hydrops fetalis, except when the fetal heart rate is persistently below 50 per minute.

Infectious Diseases

Intrauterine infections are a common cause of fetal hydrops (4 to 15%), with parvovirus B19 infection and secondary anemia the most frequent.²⁷ Fetal toxoplasmosis, syphilis, cytomegalovirus, and varicella can also present as fetal hydrops, with commonly associated findings such as hepatomegaly, splenomegaly, or ascites.^{2,28} (Tables 2 and 3) Strategies for the prenatal screening and diagnosis of maternal–fetal infections are detailed below.

Hematological Disorders

Hematological disorders can be identified in 7% of cases of NIHF. Ethnicity at increased risk of fetal thalassemia may affect this frequency. For example, homozygous alpha-thalassemia accounted for 55.1% of NIHF diagnosed after 20 weeks in Southern China.²⁹

Structural Congenital Anomalies

Structural congenital anomalies should be evaluated as they represent a large group of disorders that can be identified through detailed fetal imaging and may be treatable. A list of congenital anomalies associated with fetal hydrops is presented in Table 2. Primary chylothorax,^{2,30} congenital cystic adenomatoid malformation,³¹ various fetal tumours,³² and metabolic diseases have been also described as causal factors of hydrops.^{33,34}

Single Gene Disorders

Known single-gene disorders affecting metabolic pathways, hematological conditions, skeletal dysplasia, neurologic disorders, cardiomyopathies, congenital nephrosis, congenital lymphedema, and mitochondrial mutations have been reported as causes of potentially recurring fetal hydrops.²⁶ However, many families have

Table 3. Ultrasound findings in fetal infections causing fetal hydrops

Infection	CNS	Cardiac	Abdominal	Placental/AF	IUGR
Toxoplasmosis	+		+	+	Rare
Syphilis			+	+	Rare
Rubella	+	+	+		+
Parvovirus		+	+	+	
CMV	+	+	+	+	+
Varicella	+		+	+	+

Adapted from Klein et al.⁵²
 CNS: central nervous system; IUGR: intrauterine growth restriction

had more than one child with fetal or neonatal hydrops in whom the underlying genetic defect has not been discovered. Some genes may be expressed specifically during fetal development, while others may represent an early-onset form of a known pediatric disorder (e.g., Gaucher, fetal akinesia, glycogen storage disorder type IV).^{35,36} The identification of a single gene disorder not only helps in predicting the outcome of the current pregnancy, but also has an impact on the management or screening of future pregnancies in the family.²⁶

Recent data suggest that metabolic disorders may be responsible for some idiopathic NIHF. Lysosomal storage disorders are the group of disorders most commonly involved in NIHF. Hydrops fetalis is a relatively common presentation in mucopolysaccharidosis type VII,³⁷ infantile galactosialidosis,³⁸ type 2 Gaucher disease, and infantile free sialic acid storage disease. At least 15 other inborn errors of metabolism may cause NIHF^{34,39}: GM1 gangliosidosis, Niemann-Pick type A, Niemann-Pick type C, MPS I, MPS IVA, mucopolipidosis II, sialidosis, multiple sulfatase deficiency, Farber disease, Wolman disease, I cell disease, glycogen storage disease IV,³⁶ transaldolase deficiency,⁴⁰ Pearson syndrome (mitochondrial disorder), and congenital disorders of glycosylation. Specific enzyme assays are available to test for these disorders on cultured amniocytes or specific metabolite measurement in amniotic fluid supernatant.^{41,42}

Diagnosing or ruling out a metabolic disorder as the causal factor for NIHF is important because these single gene disorders carry a 25% risk of recurrence, and their identification may allow for prenatal diagnosis at an earlier stage in future pregnancies. Prenatal diagnosis of such conditions also facilitates postnatal management. Despite thorough investigations, earlier reports conclude that at least 28% of cases of NIHF remain unexplained²; a recent systematic review of the literature found that 17.8% were considered idiopathic.²¹

PRENATAL MANAGEMENT

Fetal hydrops mandates urgent referral to a maternal–fetal medicine specialist for rapid evaluation because some situations must be considered true prenatal medical emergencies, particularly after 16 to 18 weeks. Triage depends on gestational age, etiology, and severity. Ultrasound examination including umbilical artery and middle cerebral artery Doppler studies may guide lifesaving treatments such as in utero transfusions, fetal cardioversion, or placement of diversion shunts. Table 4 outlines the baseline investigations for all fetal hydrops. One should not wait for complete results before initiating referral, invasive diagnostic procedures, or treatments.

Clinical Evaluation

A detailed history should be taken focusing on the mother's past medical and reproductive history, including previous fetal, neonatal, or infantile deaths. A clear determination of gestational age and history of viral exposure/illness, travelling, bleeding, or use of medication during the pregnancy should be obtained. Parental past medical history, ethnic background, and consanguinity should be documented. A 3-generation pedigree, including specific questions on fetal loss, death in infancy, developmental delay, congenital malformation, genetic syndrome, skeletal dysplasia, chronic infantile illness, inherited cardiomyopathies, and neurodegenerative disorders should be completed. Maternal history, physical examination, and laboratory tests should be used to rule out developing preeclampsia (mirror syndrome) and underlying chronic illness associated with fetal hydrops (e.g., Sjogren, lupus, uncontrolled diabetes, Graves disease).

Non-invasive Testing

Timely referral to a maternal–fetal medicine specialist allows for detailed and comprehensive ultrasound examination and the early identification of any treatable causes. A careful search for structural fetal anomalies or genetic syndromes, signs of fetal infection, and evidence of umbilical cord or placental anomalies may rapidly indicate the cause of hydrops.

Table 4. Step-wise investigation of non-immune fetal hydrops**STEP 1: Urgent***Fetal imaging*

- Detailed morphology obstetrical ultrasound in a tertiary care centre and the assessment of the fetal venous and arterial circulation
- Doppler (MCA, venous, arterial)
- Fetal echocardiogram

Maternal blood

- CBC
- Kleihauer-Betke
- ABO blood type and antigen status
- Indirect Coombs (antibody screen)
- Venereal disease research laboratory test for syphilis
- Acute phase titers (parvovirus, toxoplasmosis, cytomegalovirus, rubella)
- Liver function tests, uric acid, coagulation tests (suspected mirror syndrome)
- SS-A, SS-B antibodies (fetal bradyarrhythmia)
- Depending on ethnic origin: hemoglobin electrophoresis, G6PD deficiency screen

STEP 2: Invasive / referral / treatment*Amniotic fluid*

- FISH or QF-PCR on uncultured amniocytes, followed by karyotype or microarray analysis
- PCR for CMV
- PCR for parvovirus-B19/toxoplasmosis (selected cases)
- CMV and bacterial cultures in selected cases
- Inform the laboratory to keep the amniotic cells and supernatant for future studies
- DNA extraction if alpha-thalassemia suspected
- Fetal lung maturity testing (depending on gestational age)

Fetal blood sampling (maternal fetal medicine specialist)

- CBC, white blood cell count differential, platelets
- Direct Coombs' test
- Blood group and type
- Karyotype (standard) with genetic microarray consideration
- TORCH/viral serologies
- Protein/albumin/liver function tests (not on all cases)
- Hemoglobin electrophoresis (depending on ethnicity)

Cavity aspiration (may be done at the time of amniocentesis)

- Lymphocyte count
- Protein/albumin
- Creatinin/ionogram (ascites)
- PCR for CMV and viral and bacterial cultures

Consider consultation with neonatology (depending on gestational age)

STEP 3: Post-delivery**Examination of the placenta***Neonatal survival*

- Detailed physical examination
- Cardiac monitoring
- Cranial ultrasound
- Abdominal ultrasound
- Cardiac monitoring
- Echocardiography
- CBC, liver function tests, creatinine kinase, albumin, protein
- TORCH, viral culture
- Specialized testing guided by results of prenatal work-up

Neonatal / fetal demise

- Clinical pictures
- Fetal cells culture (skin, others)
- Freeze fetal tissues and AF supernatant
- Bank fetal DNA
- Skeletal survey
- Placental pathology
- Autopsy¹⁰

Multiple mechanisms of hydrops may coexist and the primary cause is often not obvious. Determination of prognosis is important and may be achieved by a semi-quantitative measure of heart failure. Specific questions may be addressed through arterial and venous Doppler ultrasound in conjunction with fetal echocardiogram.⁴³

Doppler Ultrasound

The measurement of MCA peak systolic velocity to assess fetal anemia is essential to the management of fetuses with NIHF. After 16 weeks of gestation, there is a significant association between delta-MCA peak flow and delta hemoglobin concentration, especially when the fetal Hb concentration is very low.⁴⁴ A peak systolic above 1.5 multiples of the median has a 100% (95% CI 86 to 100%) sensitivity for detecting fetal anemia from various causes.^{4,45}

An abnormal ductus venosus waveform helps both to identify a fetus at risk for cardiac anomalies and to predict prognosis.⁴⁶ In a group of fetuses with congenital heart defects and hydrops, abnormal hepatic vein and ductus venosus blood velocities, along with umbilical venous pulsations were strongly associated with mortality.⁴⁷ The most useful predictor of perinatal death in fetal hydrops is the presence of umbilical venous pulsations, because the most common pathway of perinatal demise is fetal congestive heart failure.⁴³

Arterial Doppler is an indicator of the redistribution of fetal cardiac output affecting the blood flow in the descending aorta and in the UA. Absent or reversed end diastolic flow in the umbilical artery reflects elevated placental resistance. Absent end diastolic flow is common in non-survivors, and often associated with increased cardiac afterload.⁴⁷ Changes in UA Doppler appear later than venous Doppler and cardiac function alterations.

Fetal Echocardiogram

Fetal echocardiogram is used to assess cardiac anatomy and function. Congenital cardiac malformations are common with an underlying genetic syndrome or a chromosome anomaly. Depending on the type of the cardiac malformation, a syndromic differential diagnosis should be considered and investigated.⁴⁸

Cardiac arrhythmia may be primary or may occur secondary to a systemic etiology such as hyperthyroidism or in mothers with autoimmune conditions associated with high titers of circulating anti-SS-A or anti-SS-B antibodies.^{49,50} The two most common important fetal arrhythmias are supra-ventricular tachyarrhythmias and severe bradyarrhythmias associated with complete heart block.⁵⁰ Finally, congestive heart failure may be secondary to other systemic causes that

need to be evaluated. In fact, when identifying a cardiac component in the context of NIHF, this important finding should not be considered a final diagnosis in and of itself. A careful search for underlying maternal illness or single-gene disorder is indicated.

Enlargement of the cardiac chambers is a common sign of heart failure.⁵⁰ The right atrium is the final pathway for venous return and frequently shows enlargement in situations of relative foramen obstruction, volume overload, tricuspid valve regurgitation, and increased afterload. Normally, the ratio of the cardiac circumference over the thoracic circumference at the level of the 4-chamber view should be less than 0.5.⁵¹

Recommendation

3. Imaging studies should include comprehensive obstetrical ultrasound (including arterial and venous fetal Doppler) and fetal echocardiography. (II-2A)

Search for Fetal Infections

This section describes the different laboratory tests for infectious disorders that may present as fetal hydrops, mainly to review the limitations of these tests. Tests need to be prioritized as shown in the algorithm presented in Table 4. Fetal ultrasound may reveal a pattern of findings typical of a particular infectious agent.

Laboratory methods for the assessment of viral infections are in two categories: serology and virus or parasite detection.⁵² Serology is very sensitive but often cannot conclusively determine the time of infection, which may be critical for risk assessment. Traditional serological tests, which measure antibody levels including immunoglobulin M and immunoglobulin G, usually require two samples separated by a significant time period for determination of seroconversion or a substantial rise in titer.⁵² IgM identification is more indicative than IgG of a recent infection; however, IgM may persist several months or even years in some cases. IgM can also be negative at the time of fetal hydrops if the seroconversion occurred several weeks earlier. Various tests may distinguish between IgG and IgM and may allow diagnosis in one serum sample, but biological and technical difficulties are common and may cause false-positive and false-negative results.⁵³

Maternal toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and parvovirus B19 serologies are commonly searched for suspicion of fetal infection. A study of 476 patients in the United Kingdom found that, among TORCH agents, only CMV was commonly found as a cause of fetal ultrasound findings.⁵⁴ The archived serum from

routine first-trimester baseline tests is very useful, when available, to establish prior immune status and to document seroconversion. Testing for rare infectious diseases (syphilis, enterovirus) may be considered in particular clinical situations (ultrasound findings, HIV positive mother, clinical symptoms).

Parvovirus B19

Infection during pregnancy may affect the fetus, resulting in hydrops or fetal demise.⁵⁵ The predominant ultrasound feature in fetuses infected by Parvovirus B19 is ascites,⁴⁴ sometimes associated with poorly contractile echogenic myocardium. Early diagnosis of maternal infection will allow fetal assessment and treatment by intrauterine blood transfusion. Unfortunately, mothers are often unaware of their infection until fetal signs are observed. Confirmation of B19 infection requires laboratory assessment, which is complicated by the nature of the viral infection and immune response. Serology, using enzyme-linked immunosorbent assays, relies on recombinant antigens, and concordance is low among all commercial assays available. In the absence of a “gold standard” assay, false positive and false negative results prevail.

Furthermore, maternal IgM may have dropped below the detection limit by the time fetal hydrops is identified.⁵⁶ Viral culture is difficult and virus detection is based on various molecular assays. In spite of several studies there is no consensus regarding the most appropriate clinical specimen and method for detection of viral DNA. Currently, on practical grounds, it is recommended to use ELISA IgM and IgG assays based on recombinant conformational epitopes of polyomavirus capsid proteins 1 and 2 or polyomavirus capsid protein 2 alone, and to use amniotic fluid or fetal serum for detection of fetal infection by the most sensitive molecular methods available (nested PCR or RT-PCR).⁵⁶ Recommendations for evaluation and treatment of parvovirus infection during pregnancy have been published by the SOGC Maternal–Fetal Medicine and Infectious Diseases Committees.⁵⁷

Rubella

If the patient is not immune to rubella, serial IgG and IgM titers should be done. If congenital rubella is strongly suspected, amniotic fluid culture or fetal blood sampling for IgM determination is indicated as infection leads to severe fetal morbidity. Postnatal determination is achieved through evaluation of IgG and IgM levels, along with viral isolation.

Cytomegalovirus

CMV is excreted in the urine of the infected fetus, so detection of the virus in AF has proven to be a highly sensitive and reliable method.⁵⁸ Numerous studies have

focused on the most appropriate timing for performing amniocentesis to yield the best sensitivity for detection of fetal infection. These studies clearly indicated that AF should be collected after 21 gestational weeks and after at least 6 weeks maternal infection. Most studies state that the timing of amniocentesis is more critical for sensitivity in detecting the virus in AF than the laboratory methods used. If invasive testing is performed, PCR is the preferred method for detection of CMV in amniotic fluid. Problems with molecular contamination (false positive results) and the need to address prognostic issues led to the development of quantitative PCR assays; the highly advanced real-time PCR is the most up-to-date method.^{58,59}

Laboratory testing to determine intrauterine CMV infection involves several steps that should be done simultaneously in fetal hydrops. Maternal primary or recurrent infection is assessed by serology using IgM, IgG, and IgG-avidity assays. A second blood sample should be sought to demonstrate antibody kinetics typical of the current infection and not of a remote infection or a non-specific reaction. If maternal primary infection has been established and the pregnancy continues, prenatal diagnosis follows at 21 to 23 weeks gestation or at 6 to 9 weeks after seroconversion (if known). Detection of CMV in AF is achieved by virus culturing and/or PCR. Quantitative PCR in the amniotic fluid can determine the viral load and could be useful for the assessment of fetal impact and prognosis, although the clinical value of this test is still under investigation.⁶⁰ Further information on CMV infection in pregnancy is available in a previously published SOGC guideline.⁵⁸

Varicella-zoster virus

VZV is rarely found as a cause of fetal hydrops.⁶¹ The primary tool for assessing maternal infection is isolation of the virus from maternal lesions. Type-specific IgG assays must be applied to determine recurrent maternal infections. Antigen detection or DNA detection by PCR in skin lesion samples are additional tools for the rapid and sensitive diagnosis of symptomatic current infection. Prenatal diagnosis can be performed by PCR detection of the virus in AF, but false negative results are common and positive results do not necessarily correlate with fetal damage.⁶² Neonatal infection is diagnosed by virus culture or PCR in skin lesions or other clinical specimens in case of a disseminated form.

Other viral infections

A few studies report fetuses with NIHF caused by various subtypes of Coxsackie virus and adenovirus identified through targeted PCR amplification in affected fetal tissues.^{19,63}

Testing for Alpha-thalassemia

The most severe form of alpha-thalassemia is called Bart's disease.⁶⁴ The absence of normal copies of alpha-hemoglobin genes in a fetus causes severe anemia leading to hydrops during fetal life.⁶⁴ This autosomal recessive condition occurs at a higher frequency in some ethnic groups such as Mediterranean, African, and South-East Asian populations.⁶⁴ From a practical point of view in Canada, one can take the approach that any patient who is not Japanese, Korean, Caucasian of Northern European ancestry, First Nations, or Inuit should be screened.⁶⁴ Carriers are suspected on the basis of the presence of low red blood cell volume (microcytosis) with normal ferritin. HbH bodies identified on blood smear examination are characteristic of alpha-thalassemia carrier status. Even in the absence of HbH bodies, when microcytosis is present, molecular testing should be performed in both parents to look for the frequent deletion and rarer point mutations.

In cases suspected of alpha-thalassemia, MCA Doppler should be done to confirm anemia. When anemia is suspected, it should be confirmed by fetal blood sampling for rapid initiation of treatment (intrauterine transfusion). The diagnosis should be further confirmed by fetal DNA testing through amniocentesis or placental biopsy.⁶⁴ If fetal blood is taken by cordocentesis, Hb Bart's can be identified. When confirmed, parents should be informed of the poor prognosis and counselled about the 25% recurrence risk and the availability of invasive prenatal diagnosis for future pregnancies. Intrauterine transfusion in affected fetuses has been reported with various results.⁶⁵

Invasive Investigation

Fetal karyotyping and genetic microarray molecular testing should be conducted in all cases of unexplained NIHF. Cytogenetic laboratories can provide a preliminary result of the fetal karyotype within 24 to 48 hours using QF-PCR or FISH techniques (amniotic fluid), direct analysis (placental biopsy), or conventional karyotyping (fetal blood).

Amniotic fluid should also be obtained for viral and bacterial cultures, viral/parasitic-specific PCR studies, and karyotyping. In selected cases, the supernatant can be used for biochemical studies.^{34,66} Amniotic cells should be kept in culture for future studies and DNA extraction or frozen for later analysis.

Fetal blood sampling to determine fetal hemoglobin levels may be performed under the following circumstances: MCA Doppler results suggestive of fetal anemia, documented parvovirus B19 seroconversion,

parental microcytic anemia from at risk-ethnicity, and documented fetal bleeding. Baseline studies to consider on fetal blood sampling include CBC, platelets, direct Coombs' test, blood group, karyotype, TORCH/parvovirus B19 (IgM), and albumin. If fetal anemia is strongly suspected, O-negative CMV-negative maternally cross-matched blood should be ready for transfusion. In specific situations (positive family history, recurring hydrops), targeted metabolic investigations may also be performed. For example, fetal blood sample was used to diagnose a congenital disorder of glycosylation type Ia in a 27-week fetus with NIHF.⁶⁷ The fetal loss rate after cordocentesis was 11.32% in a group of hydropic fetuses, probably due in part to the high loss rate associated with hydrops itself.⁶⁸

Specific enzyme assays are available to test for lysosomal storage disorders on cultured amniocytes (N-acetylglucosaminase-6S-sulfatase, beta-glucuronidase, beta-galactosidase, beta-glucosidase, alpha-iduronidase, a-D-neuraminidase, sphingomyelinase) or specific metabolite measurement in amniotic fluid supernatant (total hexosaminidase, betaglucuronidase, alpha-mannosidase, chitotriosidase).^{41,42} These assays must be performed by a specialized biochemical genetics laboratory. The recommended metabolic investigation for unexplained fetal hydrops is shown in Table 5. The laboratory should be informed of the need to keep frozen supernatant and amniotic cells for future studies. Diagnosing a metabolic disorder as the causal factor for NIHF is important because these single-gene disorders carry a 25% recurrence risk. Their identification may allow for prenatal diagnosis at an earlier stage in future pregnancies.^{26,41} Prenatal diagnosis of such conditions also facilitates postnatal management. Fetal cavity aspiration may be used as a diagnostic and therapeutic measure. A lymphocyte count (pleural effusion, cystic hygroma), biochemical studies, protein/albumin determination, histology, and viral and bacterial cultures are indicated.^{26,41}

Recommendations

- Investigation for maternal–fetal infections, and alpha-thalassemia in women at risk because of their ethnicity, should be performed in all cases of unexplained fetal hydrops (II-2A).
- To evaluate the risk of fetal anemia, Doppler measurement of the middle cerebral artery peak systolic velocity should be performed in all hydropic fetuses after 16 weeks of gestation. In case of suspected fetal anemia, fetal blood sampling and intrauterine transfusion should be offered rapidly. (II-2A)

Table 5. Lysosomal enzymatic assays used for NIHF

a.	Beta-galactosidase (GM1)
b.	Beta-glucuronidase (MPS VII)
c.	Beta-glucosidase (Gaucher)
d.	Neuraminidase (sialidase)
e.	Beta-galactosidase and neuraminidase (galactosialidase)
f.	Sphingomyelinase (Niemann-Pick A and B)
g.	Mucopolipidosis type II

PROGNOSIS

NIHF from all causes has a high mortality rate. Fetal chromosomal anomaly, gestational age < 24 weeks and fetal structural anomalies other than chylothorax are indicators of a poor prognosis. However, fetal treatment has significantly improved survival in selected cases.

When a pregnancy is continued with known fetal hydrops, the occurrence of maternal “mirror” syndrome should be carefully monitored. Mirror syndrome, also referred to as Ballantyne’s syndrome, is defined as the development of maternal edema secondary to fetal hydrops.^{21,69} Severe preeclampsia is usually associated with the syndrome. Because the maternal prognosis can be poor, the option of continuing a pregnancy with fetal hydrops should be carefully discussed.

Excluding chromosomal abnormalities, the survival rate of NIHF is about 31% to 48%.⁷ Most of the causes, a large proportion of which are lethal disorders, respond poorly to therapy. Without treatment the prognosis is generally poor, except in the rare case of spontaneous resolution of parvovirus B19 infection.⁷⁰

In a series of 38 cases of NIHF, Negishi et al. reported a 23% survival rate in the treatment group.³⁰ The presence of a chromosomal anomaly, along with an earlier age at detection of NIHF, was associated with a poorer outcome. In a series of 30 cases of NIHF diagnosed between 10 and 14 weeks of gestation, all cases resulted in spontaneous abortion, intrauterine fetal death, or pregnancy termination.²³ In another series of 45 cases diagnosed between 11 and 17 weeks, only 2 resulted in a normal outcome.⁷¹ McCoy et al. reported a survival rate of < 5% for infants with hydrops diagnosed before 24 weeks of gestation and 20% survival for infants diagnosed after 24 weeks of gestation.¹⁹

In a report on 23 women with NIHF, termination of pregnancy was performed for 10 chromosomal and 5 structural abnormalities, and there was one intrauterine

fetal death.⁷² One baby with diaphragmatic hernia died in the neonatal period from pulmonary hypoplasia despite reversal of hydrops by in utero shunting, and one baby with treated polyhydramnios was born at 30 weeks and died on day 5. The remaining 5 cases, in which structural and chromosomal abnormalities were excluded, had fetal therapy between 22 and 32 weeks’ gestation (4 shunt insertions, 1 blood transfusion) and in all the hydrops reversed and the pregnancy continued to at least 35 weeks’ gestation. All 5 neonates were discharged from hospital alive and well. Fetal therapy in cases of NIHF with normal structure and karyotype was associated with a very good outcome.⁷²

Two recent studies address the issues of postnatal survival in live-born neonates with hydrops. Data from a large national database⁷³ reveals that mortality rates were highest among neonates with congenital anomalies (57.7%) and lowest among neonates with congenital chylothorax (5.9%). Factors associated with death were younger gestational age, low 5-minute Apgar score, and need for high levels of support during the first 24 hours of life (high oxygen needs and high-frequency ventilation). Of the 597 neonates included in the study, 115 were transferred from another hospital, 215 died before discharge, and 267 were discharged from the hospital.⁷³ Huang et al. reported a 50% survival rate in a group of 28 live-born neonates with NIHF.⁷⁴ The survival rate was 83% in infants with lymphatic malformations. Preterm birth at less than 34 weeks and low serum albumin concentration were two poor prognostic factors for survival.⁷⁴

Few studies have examined the long-term outcome of NIHF identified prenatally. Breur et al. reported normal neurodevelopmental outcomes in 5 children who presented with fetal heart block and hydrops fetalis. In his series of 10 fetuses, 3 died in utero, 2 died from dilated cardiomyopathy at age 9 months and 4 years, and 5 survived.⁷⁵

These results demonstrate that the prognosis of NIHF differs markedly between different etiological groups. It is essential to attempt to identify the etiology to better predict prognosis, offer prenatal treatment when available, and deliver in a tertiary perinatal care centre to improve postnatal outcome.

Recommendation

- All cases of unexplained fetal hydrops should be referred to a medical genetics service where available. Detailed postnatal evaluation by a medical geneticist should be performed on all cases of newborns with unexplained non-immune hydrops. (II-2A)

Table 6. Fetal therapies for non-immune hydrops

1. Intrauterine transfusion for anemia
 - Maternal acquired pure red cell aplasia
 - Maternal fetal hemorrhage
 - Fetal hemolysis (G6PD)
 - Fetal parvovirus infection
2. Repeated centesis or shunt insertion
 - Pleural effusion
 - Ascitis
 - Thoracic cystic lesions
 - Congenital cystic adenomatoid malformation
 - Pulmonary sequestration
 - Pulmonary lymphangiectasia
3. Intravascular or maternal treatment with anti-arrhythmic drugs
 - Fetal tachyarrhythmia
 - Atrioventricular block (anti-SS-A/SS-B)
4. Fetal procedures: open fetal surgery or laser vessel ablation/radio frequency ablation
 - Congenital cystic adenomatoid malformation
 - Sequestration
 - Sacrococcygeal teratoma
 - Twin-to-twin transfusion syndrome (stage IV)
5. Others
 - Antithyroid drugs (fetal thyrotoxicosis)

PERINATAL MANAGEMENT

Fetal Treatment

Fetal hydrops is a medical emergency that mandates urgent referral to a maternal–fetal medicine specialist and a medical geneticist for rapid evaluation. The hydropic fetus is usually in a precarious state and even minimal delays may prevent access to life-saving procedures.

Fetal treatment options for NIHF depend on the etiology and the gestational age at diagnosis. A maternal–fetal specialist should undertake this evaluation. Options available consist of:

1. intrauterine transfusion for anemia,
2. repeated centesis or shunt insertion for pleural effusion, ascites, or thoracic cystic lesions,
3. intravascular or maternal treatment with anti-arrhythmic drugs to treat fetal tachyarrhythmia, in close collaboration with cardiologists,
4. laser surgery for severe and early twin-to-twin transfusion syndrome with hydrops (stage IV), and
5. open fetal surgery where available, or laser or radiofrequency ablation for major structural anomalies associated with NIHF (Table 6).

Fetuses diagnosed with a treatable cause of NIHF should be delivered in a tertiary care centre with prenatal consultation with appropriate subspecialties including maternal–fetal medicine specialists, geneticists, neonatologists, and pediatric surgeons. Antenatal consultation allows for parental counselling, adequate preparation of the resuscitation team, and planning of specialized equipment required in the delivery room. Pre-delivery cavity aspiration (pleural effusions, severe ascitis, severe polyhydramnios) by the perinatologist may facilitate neonatal management and reduce maternal complications. Postnatal therapy begins with vigorous resuscitation including thoracocentesis and/or paracentesis to establish adequate lung expansion; this is followed by efforts to determine the cause and correct the condition responsible for the hydrops. Once the neonate is stabilized, a detailed physical examination, cardiac monitoring, chest radiograph, and ultrasound examinations (head, cardiac, and abdominal) are performed. Additional testing is guided by the investigation initiated antenatally.⁵

Postmortem Evaluation (Fetus and Placenta)

It is mandatory to continue the investigation after the death of the fetus or newborn with NIHF. Referral to a genetic service should be made to plan for additional investigation. Clinical photography and fetal X-rays should be obtained

to evaluate possible dysmorphic syndrome or skeletal dysplasia. Autopsy should be strongly recommended, at least for non-chromosomal cases.^{10,76} Storage of fetal blood, tissue, DNA, and amniotic fluid supernatant should be collected in the appropriate tube and setting (i.e. frozen at -70°C). The preservation of a potentially dividing fetal cell line (amniocytes, skin biopsy) is indicated for future biochemical or molecular genetic testing. Extensive sampling from various sources is necessary to test for tissue-specific enzymatic activity or gene expression. Placental examination (microscopy, histopathology) focusing on tumours, fetal anemia, infection, and metabolic disorder is indicated.⁷⁷

Recommendation

7. Autopsy should be recommended in all cases of fetal or neonatal death or pregnancy termination. (II-2A)
Amniotic fluid and/or fetal cells should be stored for future genetic testing. (II-2B)

CONCLUSION

The prognosis of NIHF differs markedly between different etiological groups. Recent progress in prenatal genetics and maternal–fetal medicine provides us with newer tools to identify the underlying etiology. Prompt access to maternal–fetal medicine units for fetal evaluation and treatment has improved outcomes. It is essential to attempt to identify the etiology to better predict prognosis, offer treatment when appropriate, and assess recurrence risk to plan for the management of future pregnancies.

REFERENCES

1. Machin GA. Hydrops revisited: literature review of 1,414 cases published in the 1980s. *Am J Med Gen A* 1989;34:366–90.
2. Machin GA. Hydrops, cystic hygroma, hydrothorax, pericardial effusion and fetal ascites. In: Gilbert-Barnes E, ed. *Potter's pathology of the fetus and infant*. St-Louis: Mosby; 1997.
3. Fung Kee Fung K, Eason E, Crane J, Armson A, De La Ronde S, Farine D, et al; SOGC Maternal-Fetal Medicine Committee; SOGC Genetics Committee. Prevention of Rh alloimmunization. SOGC Clinical Practice Guidelines, No. 133, September 2003. *J Obstet Gynaecol Can* 2003;25:765–73.
4. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. *N Engl J Med* 2000;342:9–14.
5. Hansen T. Non immune hydrops fetalis. In: Rudolph A, Kamei R, Overby K, eds. *Rudolph's pediatrics*. 21st ed. New York: McGraw-Hill; 2003.
6. Ismail KM, Martin WL, Ghosh S, Whittle MJ, Kilby MD. Etiology and outcome of hydrops fetalis. *J Matern Fetal Med* 2001;10:175–81.
7. Milunsky A. *Genetic disorders of the fetus: diagnosis, prevention and treatment*. 5th ed. Baltimore: John Hopkins University Press; 2004.
8. Kharat R, Yamamoto M, Roume J, Couderc S, Vialard F, Hillion Y, et al. Karyotype and outcome of fetuses diagnosed with cystic hygroma in the first trimester in relation to nuchal translucency thickness. *Prenat Diagn* 2006;26:369–72.
9. Molina FS, Avgidou K, Kagan KO, Poggi S, Nicolaides KH. Cystic hygromas, nuchal edema, and nuchal translucency at 11–14 weeks of gestation. *Obstet Gynecol* 2006;107:678–83.
10. Desilets V, Oligny LL; Genetics Committee of the Society of Obstetricians and Gynaecology Canada; Family Physicians Advisory Committee; Medico–Legal Committee of the SOGC. Fetal and perinatal autopsy in prenatally diagnosed fetal abnormalities with normal karyotype. SOGC Clinical Practice Guidelines, No. 267, October 2011. *J Obstet Gynaecol Can* 2011;33:1047–57.
11. Gagnon A, Wilson RD, Allen VM, Audibert F, Blight C, Brock JA, et al; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada. Evaluation of prenatally diagnosed structural congenital anomalies. SOGC Clinical Practice Guidelines, No. 234, September 2009. *J Obstet Gynaecol Can* 2009;31:875–81.
12. Chitayat D, Langlois S, Wilson RD; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for fetal aneuploidy in singleton pregnancies. SOGC Clinical Practice Guidelines, No. 261, July 2011. *J Obstet Gynaecol Can* 2011;33:736–50.
13. Morin L, Lim K; SOGC Diagnostic Imaging Committee. Ultrasound in twin pregnancies. SOGC Clinical Practice Guidelines, No. 260, June 2011. *J Obstet Gynaecol Can* 2011;33:643–56.
14. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med* 2004;351:136–44.
15. Yamamoto M, Ville Y. Twin-to-twin transfusion syndrome: management options and outcomes. *Clin Obstet Gynecol* 2005;48:973–80.
16. Chalouhi GE, Stirnemann JJ, Salomon LJ, Essaoui M, Quibel T, Ville Y. Specific complications of monochorionic twin pregnancies: twin-twin transfusion syndrome and twin reversed arterial perfusion sequence. *Semin Fetal Neonatal Med* 2010;15:349–56.
17. Audibert F, Gagnon A; SOGC Genetics Committee; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for and diagnosis of aneuploidy in twin pregnancies. SOGC Clinical Practice Guidelines, No. 262, July 2011. *J Obstet Gynaecol Can* 2011;33:754–67.
18. Bellini C, Hennekam RC, Bonioli E. A diagnostic flow chart for non-immune hydrops fetalis. *Am J Med Genet A* 2009;149A:852–3.
19. McCoy MC, Katz VL, Gould N, Kuller JA. Non-immune hydrops after 20 weeks' gestation: review of 10 years' experience with suggestions for management. *Obstet Gynecol* 1995;85:578–82.
20. Santo S, Mansour S, Thilaganathan B, Homfray T, Papageorgiou A, Calvert S, et al. Prenatal diagnosis of non-immune hydrops fetalis: what do we tell the parents? *Prenat Diagn* 2011;31:186–95.
21. Braun T, Brauer M, Fuchs I, Czernik C, Dudenhausen JW, Henrich W, et al. Mirror syndrome: a systematic review of fetal associated conditions, maternal presentation and perinatal outcome. *Fetal Diagn Therapy* 2010;27:191–203.
22. Jauniaux E, Van Maldergem L, De Munter C, Moscoso G, Gillerot Y. Nonimmune hydrops fetalis associated with genetic abnormalities. *Obstet Gynecol* 1990;75:568–72.
23. Has R. Non-immune hydrops fetalis in the first trimester: a review of 30 cases. *Clin Exp Obstet Gynecol* 2001;28:187–90.
24. Wapner RJ, Driscoll DA, Simpson JL. Integration of microarray technology into prenatal diagnosis: counselling issues generated during the NICHD clinical trial. *Prenat Diagn* 2012;32:396–400.

25. Knilans TK. Cardiac abnormalities associated with hydrops fetalis. *Semin Perinatol* 1995;19:483–92.
26. Bellini C, Hennekam RC. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. *Am J Med Genet A* 2012;158A:597–605.
27. de Jong EP, Walther FJ, Kroes AC, Oepkes D. Parvovirus B19 infection in pregnancy: new insights and management. *Prenat Diagn* 2011;31:419–25.
28. Crino JP. Ultrasound and fetal diagnosis of perinatal infection. *Clin Obstet Gynecol* 1999;42:71–80; quiz 174–5.
29. Liao C, Xie XM, Li DZ. Two cases of homozygous alpha0-thalassemia diagnosed prenatally in pregnancies at risk for beta-thalassemia in China. *Ultrasound Obstet Gynecol* 2007;29:474–5.
30. Negishi H, Yamada H, Okuyama K, Sagawa T, Makinoda S, Fujimoto S. Outcome of non-immune hydrops fetalis and a fetus with hydrothorax and/or ascites: with some trials of intrauterine treatment. *J Perinat Med* 1997;25:71–7.
31. Yong PJ, von Dadelszen P, Carpara D, Lim K, Kent N, Tessier F, et al. Prediction of pediatric outcome after prenatal diagnosis and expectant antenatal management of congenital cystic adenomatoid malformation. *Fetal Diagn Ther* 2012;31:94–102.
32. Isaacs H Jr. Fetal hydrops associated with tumors. *Am J Perinatol* 2008;25:43–68.
33. Norton ME. Nonimmune hydrops fetalis. *Semin Perinatol* 1994;18:321–32.
34. Kooper AJ, Janssens PM, de Groot AN, Liebrand-van Sambeek ML, van den Berg CJ, Tan-Sindhunata GB, et al. Lysosomal storage diseases in non-immune hydrops fetalis pregnancies. *Clin Chim Acta* 2006;371:176–82.
35. Gort L, Granell MR, Fernandez G, Carreto P, Sanchez A, Coll MJ. Fast protocol for the diagnosis of lysosomal diseases in nonimmune hydrops fetalis. *Prenat Diagn* 2012;32:1139–42.
36. L'Hermine-Coulomb A, Beuzen F, Bouvier R, Rolland MO, Froissart R, Menez F, et al. Fetal type IV glycogen storage disease: clinical, enzymatic, and genetic data of a pure muscular form with variable and early antenatal manifestations in the same family. *Am J Med Genet A* 2005;139A:118–22.
37. Venkat-Raman N, Sebire NJ, Murphy KW. Recurrent fetal hydrops due to mucopolysaccharidoses type VII. *Fetal Diagn Ther* 2006;21:250–4.
38. Carvalho S, Martins M, Fortuna A, Ramos U, Ramos C, Rodrigues MC. Galactosialidosis presenting as nonimmune fetal hydrops: a case report. *Prenat Diagn* 2009;29:895–6.
39. Saudubray J, Van der Berghe G, Walter J. *Inborn metabolic diseases: diagnosis and treatment*. Berlin: Springer-Verlag; 2007.
40. Valayannopoulos V, Verhoeven NM, Mention K, Salomons GS, Sommelet D, Gonzales M, et al. Transaldolase deficiency: a new cause of hydrops fetalis and neonatal multi-organ disease. *J Pediatr* 2006;149:713–7.
41. Burin MG, Scholz AP, Gus R, Sansaverino MT, Fritsch A, Magalhães JA, et al. Investigation of lysosomal storage diseases in nonimmune hydrops fetalis. *Prenat Diagn* 2004;24:653–7.
42. Stone DL, Sidransky E. Hydrops fetalis: lysosomal storage disorders in extremis. *Adv Pediatr* 1999;46:409–40.
43. Huhta JC. Guidelines for the evaluation of heart failure in the fetus with or without hydrops. *Pediatr Cardiol* 2004;25:274–86.
44. Hernandez-Andrade E, Scheier M, Dezerega V, Carmo A, Nicolaidis KH. Fetal middle cerebral artery peak systolic velocity in the investigation of non-immune hydrops. *Ultrasound Obstet Gynecol* 2004;23:442–5.
45. Mari G. Middle cerebral artery peak systolic velocity for the diagnosis of fetal anemia: the untold story. *Ultrasound Obstet Gynecol* 2005;25:323–30.
46. Cosmi E, Dessole S, Uras L, Capobianco G, D'Antona D, Andrisani A, et al. Middle cerebral artery peak systolic and ductus venosus velocity waveforms in the hydropic fetus. *J Ultrasound Med* 2005;24:209–13.
47. Hofstaetter C, Hansmann M, Eik-Nes SH, Huhta JC, Luther SL. A cardiovascular profile score in the surveillance of fetal hydrops. *J Matern Fetal Neonatal Med* 2006;19:407–13.
48. Pajkrt E, Weisz B, Firth HV, Chitty LS. Fetal cardiac anomalies and genetic syndromes. *Prenat Diagn* 2004;24:1104–15.
49. Eliasson H, Sonesson SE, Sharland G, Granath F, Simpson JM, Carvalho JS, et al; Fetal Working Group of the European Association of Pediatric Cardiology. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation* 2011;124:1919–26.
50. Fouron JC. Fetal arrhythmias: the Saint-Justine hospital experience. *Prenat Diagn* 2004;24:1068–80.
51. Berg C, Geipel A, Kohl T, Breuer J, Germer U, Krapp M, et al. Atrioventricular block detected in fetal life: associated anomalies and potential prognostic markers. *Ultrasound Obstet Gynecol* 2005;26:4–15.
52. Klein JO, Baker CJ, Remington JS, Wilson CB. Current concepts of infections of the fetus and newborn infant. In: Remington JS, Klein JO, Wilson CB, Baker CJ, eds. *Infectious diseases of the fetus and newborn infant*. Philadelphia: Elsevier Saunders; 2006: pp. 3–25.
53. Mendelson E, Aboudy Y, Smetana Z, Tepperberg M, Grossman Z. Laboratory assessment and diagnosis of congenital viral infections: rubella, cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), parvovirus B19 and human immunodeficiency virus (HIV). *Reprod Toxicol* 2006;21:350–82.
54. Abdel-Fattah SA, Bhat A, Illanes S, Bartha JL, Carrington D. TORCH test for fetal medicine indications: only CMV is necessary in the United Kingdom. *Prenat Diagnosis* 2005;25:1028–31.
55. Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. *Prenat Diagn* 2004;24:513–8.
56. Enders M, Schalasta G, Baisch C, Weidner A, Pukkila L, Kaikkonen L, et al. Human parvovirus B19 infection during pregnancy—value of modern molecular and serological diagnostics. *J Clin Virol* 2006;35:400–6.
57. Crane J; SOGC Fetal Medicine Committee. Parvovirus B19 infection in pregnancy. SOGC Clinical Practice Guidelines, No. 119, September 2002. *J Obstet Gynaecol Can* 2002;24:727–43; quiz 44–6.
58. Yinon Y, Farine D, Yudin MH, Gagnon R, Hudon L, Basso M, et al. SOGC Fetal Medicine Committee. Cytomegalovirus infection in pregnancy. SOGC Clinical Practice Guidelines, No. 240, April 2010. *J Obstet Gynaecol Can* 2010;32:348–54.
59. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. *Obstet Gynecol Surv* 2010;65:736–43.
60. Lazzarotto T, Gabrielli L, Foschini MP, Lanari M, Guerra B, Eusebi V, et al. Congenital cytomegalovirus infection in twin pregnancies: viral load in the amniotic fluid and pregnancy outcome. *Pediatrics* 2003;112:e153–e157.
61. Harger JH, Ernest JM, Thurnau GR, Moawad A, Thom E, Landon MB, et al; National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. *Obstet Gynecol* 2002;100:260–5.
62. Mouly F, Mirlesse V, Meritet JF, Rozenberg F, Poissonier MH, Lebon P, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. *Am J Obstet Gynecol* 1997;177:894–8.

63. Bachmaier N, Fusch C, Stenger RD, Grabow D, Mentel R, Warzok R. Nonimmune hydrops fetalis due to enterovirus infection. *Eur J Obstet Gynecol Reprod Biol* 2009;142:83–4.
64. Langlois S, Ford JC, Chitayat D, Désilets VA, Farrell SA, Geraghty M, et al.; CCMG Prenatal Diagnosis Committee; SOGC Genetics Committee. Carrier screening for thalassemia and hemoglobinopathies in Canada. *J Obstet Gynaecol Can* 2008;30:950–71.
65. Dwinell SJ, Coad S, Butler B, Albersheim S, Wadsworth LD, Wu JK, et al. In Utero diagnosis and management of a fetus with homozygous α -Thalassemia in the second trimester: a case report and literature review. *J Pediatr Hematol Oncol* 2011;33:e358–e360.
66. Ramsay SL, Maire I, Bindloss C, Fuller M, Whitfield PD, Piraud M, et al. Determination of oligosaccharides and glycolipids in amniotic fluid by electrospray ionisation tandem mass spectrometry: in utero indicators of lysosomal storage diseases. *Mol Genet Metab* 2004;83:231–8.
67. Edwards M, McKenzie F, O'Callaghan S, Somerset D, Woodford P, Spilsbury J, et al. Prenatal diagnosis of congenital disorder of glycosylation type Ia (CDG-Ia) by cordocentesis and transferrin isoelectric focussing of serum of a 27-week fetus with non-immune hydrops. *Prenat Diagn* 2006;26:985–8.
68. Acar A, Balci O, Gezginc K, Onder C, Capar M, Zamani A, et al. Evaluation of the results of cordocentesis. *Taiwan J Obstet Gynecol* 2007;46:405–9.
69. Gedikbasi A, Oztarhan K, Gunenc Z, Yildirim G, Arslan O, Yildirim D, et al. Preeclampsia due to fetal non-immune hydrops: mirror syndrome and review of literature. *Hypertens Pregnancy* 2011;30:322–30.
70. Kelly T, Mathers A. Early presentation and spontaneous resolution of hydrops fetalis, secondary to parvovirus B19 infection. *J Obstet Gynaecol* 1998;18:190–1.
71. Iskaros J, Jauniaux E, Rodeck C. Outcome of nonimmune hydrops fetalis diagnosed during the first half of pregnancy. *Obstet Gynecol* 1997;90:321–5.
72. Ayida GA, Soothill PW, Rodeck CH. Survival in non-immune hydrops fetalis without malformation or chromosomal abnormalities after invasive treatment. *Fetal Diagn Ther* 1995;10:101–5.
73. Abrams ME, Meredith KS, Kinnard P, Clark RH. Hydrops fetalis: a retrospective review of cases reported to a large national database and identification of risk factors associated with death. *Pediatrics* 2007;120:84–9.
74. Huang HR, Tsay PK, Chiang MC, Lien R, Chou YH. Prognostic factors and clinical features in liveborn neonates with hydrops fetalis. *Am J Perinatol* 2007;24:33–8.
75. Breur JM, Gooskens RH, Kapusta L, Stoutenbeek P, Visser GH, van den Berg P, et al. Neurological outcome in isolated congenital heart block and hydrops fetalis. *Fetal Diagn Ther* 2007;22:457–61.
76. Rodríguez MM, Bruce JH, Jiménez XF, Romaguera RL, Bancalari E, García OL, et al. Nonimmune hydrops fetalis in the liveborn: series of 32 autopsies. *Pediatric and developmental pathology* 2005;8:369–78.
77. Knisely AS. The pathologist and the hydropic placenta, fetus, or infant. *Semin Perinatol* 1995;19:525–31.
78. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 2003;169:207–8.