Fetal hydrops – A review and a clinical approach to identifying the cause.

Esther Dempsey[a], Tessa Homfray[b], John M Simpson[c], Steve Jeffery[a], Sahar Mansour[a,b], Pia Ostergaard[a]

[a] Molecular and Clinical Sciences, St George's University of London, London, UK

[b] SW Thames Regional Genetics Department, St George's University Hospitals NHS Foundation Trust, London, UK

[c] Department of Congenital Heart Disease, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London UK

Academic qualifications and job titles of all authors:

Esther Dempsey: 0000-0002-7653-4653 BSc, MSc, MBBS, MRCPCH. Clinical Research Fellow.

Tessa Homfray: 0000-0002-9981-9678. Consultant in Clinical Genetics, FRCP

John Simpson: 0000-0002-9773-7441. MD FRCP . Professor of Paediatric and Fetal Cardiology, Evelina London Children's Hospital.

Steve Jeffery: 0000-0003-1369-6951. BSc, MSc, PhD. Emeritus Professor.

Sahar Mansour: 0000-0001-6629-4118. Professor of Clinical Genetics, FRCP

Pia Ostergaard: 0000-0002-2190-1356. BSc, MSc, PhD. Associate Professor.

Corresponding author: Dr Esther Dempsey, Molecular and Clinical Sciences, St. George's University of London, Cranmer Terrace, London SW17 0RE, UK. email: esther.dempsey@nhs.net

Article highlights:

- Fetal hydrops is the abnormal accumulation of fluid in two or more extravascular fetal compartments.
- Fetal hydrops confers a high risk of morbidity and mortality.
- Fetal hydrops can be divided into immune (largely materno-fetal alloimmunisation) and non-immune.
- Non-immune fetal hydrops can be caused by a multitude of different causes including infection, congenital malformation, chromosome abnormalities and single-gene disorders.
- The identification of fetal anaemia from the second trimester is crucial to guiding further investigations.
- Many cases of fetal hydrops remain undiagnosed and we believe a significant proportion of these have underlying genetic lymphatic dysplasias.
- As exome or whole genome sequencing becomes increasingly available, genetic testing will feature earlier in the diagnostic pathway.

Abstract

Introduction: Fetal hydrops describes abnormal fluid accumulation in two or more extravascular fetal compartments. It is a poor prognostic sign in a fetus, and many will not survive to term. Fetal hydrops is a clinical sign rather than a diagnosis and has a multitude of different causes.

Areas covered: This review focusses on non-immune fetal hydrops. We discuss in detail the most common aetiologies such as infection and chromosomal abnormalities and cover rarer presentations of congenital malformation and single-gene disorders. We present a decision tree for the investigation of affected pregnancies.

Expert Opinion: The current approach to the investigation of fetal hydrops largely revolves around identifying the abnormal pathophysiology via ultrasound imaging. We believe that as genomic testing of a pregnancy can be undertaken with increasing accuracy, speed, accessibility and at reduced cost, genetic testing will feature earlier in the future diagnostic pathway.

1. Introduction

Fetal hydrops, the abnormal accumulation of fluid in two or more fetal compartments, affects approximately 1 in 1,700 pregnancies [1]. Fetal hydrops can occur at any point in a pregnancy. In the first trimester the first sign is typically a raised nuchal translucency on fetal ultrasound. The nuchal translucency is the region of the back of the fetal neck which increases in size when there is subcutaneous oedema or enlarged jugular lymphatic sacs (Figure 1). When there are two or more of: pericardial effusion, pleural effusion, ascites or generalised skin oedema, fetal hydrops can be diagnosed. (Figure 2). Placental thickening/oedema and polyhydramnios (increased amniotic fluid levels) can be seen in cases of fetal hydrops, but are not critical features for the diagnosis. The identification of fetal hydrops should prompt urgent referral to a centre with maternal-fetal medicine expertise. Ultrasound imaging (including Doppler studies), as well as a thorough maternal obstetric and family history, can help to make a diagnosis, guide treatment and estimate prognosis.

In a study of 167 hydropic fetuses (all causes), 66% died before or shortly after birth [2]. In a Japanese study of 214 cases of 'non-immune fetal hydrops' (discussed below), 91 (43%) survived the perinatal period, 79 (37%) were alive at one year of age and only 30 of the 58 (52%) followed for more than one year had age-appropriate neuro development [3]. Thus, fetal hydrops is an important indicator of mortality and morbidity.

Fetal hydrops is a sign, rather than a diagnosis in its own right. As such it is essential to attempt to identify the underlying cause of the hydrops. In some cases, knowledge of the underlying cause will allow for the prompt instigation of treatment, which will have a positive impact on fetal survival or inform neonatal care. In other cases, knowledge of an

underlying genetic abnormality will provide useful information to the parents about the prognosis for the pregnancy/child and the recurrence risk for future pregnancies.

Many excellent papers discuss the varied aetiologies of fetal hydrops. Most attempt to classify the underlying diagnosis into broad system-specific categories. This is fraught with difficulty as many conditions overlap and could be justifiably placed in a number of different categories. For example, fetuses with monosomy X (Turner Syndrome) could be described as chromosomal, lymphatic, cardiac and syndromic. This paper approaches the aetiology from a clinical perspective.

2. Pathophysiology of fetal hydrops

Fetal hydrops follows the same physiological rules as any other oedema. Oedema is an excess of interstitial fluid and can develop in the subcutis, lungs (pulmonary oedema), abdominal cavity (ascites), or other body cavities (pleural or pericardial effusions) [4]. Oedema occurs when capillary filtration rate exceeds lymph drainage rate for a period of time. Oedema can therefore occur from a raised capillary filtration rate, or reduced lymph drainage rate, or a combination of the two. Circumstances in which these scenarios occur are as follows [5]:

2.1 '*Impairment of lymphatic drainage'*

Lymphatic drainage is the rate limiting step for all oedema [6]. Lymph fluid re-joins the venous circulation at the junction of the subclavian and internal jugular veins. Impairment of lymphatic flow can result from malformation of the lymphatic system, compression of lymph vessels from an external mass or reduced flow due to reduced fetal movements and

so lead to fetal oedema. In a report of 79 fetuses affected by fetal akinesia sequence 31.3 % developed hydrops [7].

2.2 *'Increase in hydrostatic capillary pressure'*

An increase in hydrostatic capillary pressure changes the Starling forces in favour of increased microvascular filtration and therefore increased lymph production. An increase in hydrostatic capillary pressure results from an increase in venous pressure owing to obstruction of venous drainage or increase in central venous pressure. This leads to greater amounts of fluid filtering from the blood circulation into the interstitium. Conditions leading to increased capillary hydrostatic pressure include some congenital heart disease (arrhythmias and cardiomyopathy), vascular malformations and anaemia (causing high output heart failure) [5].

2.3 *'Reduction in intravascular osmotic pressure'*

Intravascular proteins exert an osmotic pressure, which control how much fluid leaves the circulation. In states of hypoproteinaemia, the colloid osmotic pressure of the blood is decreased, and less fluid is retained within the circulation but released into the interstitium leading to oedema. Inborn errors of metabolism and nephrotic syndrome are the most likely potential causes of hypoproteinaemia in the fetus [8].

2.4 *'Damage to peripheral capillary integrity'*

The blood capillary wall has a basic level of leakiness (permeability) to fluids and small solutes, which increases in inflammatory states. Fetal anaemia (in addition to uteroplacental insufficiency) leads to anoxic damage to cells and decreased capillary wall integrity [9]. With

increased capillary permeability, proteins leak into the interstitium causing an increase of the interstitial colloid osmotic pressure, which in turn leads to increased fluid loss from the blood capillaries into the interstitium and resultant oedema.

3. Identification of the cause of hydrops

We have presented the causes of fetal hydrops within a clinical decision framework. Figure 3 describes the process by which a clinician will prioritise investigations in an attempt to identify the cause of hydrops when presented with an affected pregnancy. In the first trimester fetal hydrops usually results from chromosome abnormalities and microarray CGH, via an invasive test of the pregnancy, is a first line investigation. From the second trimester the number of potential causes of fetal hydrops is great and investigation usually starts with the measurement of the middle cerebral artery to identify the peak systolic velocity (MCV-PSV). Where the MCV-PSV is high further investigations can be targeted toward the identification of the cause of fetal anaemia. Where the MCV-PSV is normal, and the fetus is not anaemic, ultrasound examination can be used to identify those fetuses with thoracic space occupying lesions and those with primary cardiac abnormalities. Those fetuses without space occupying lesions or primary cardiac abnormalities can be investigated on the basis of the ultrasound phenotype and are the group most likely to benefit from genomic sequencing. See Figure 3 for a diagrammatic representation of this investigatory pathway.

4. Evidence of Fetal Anaemia

Evidence of fetal anaemia will lead to further investigations as outlined below. (Figure 3).

4.1 Immune Fetal Hydrops

4.1.1 Rhesus alloimmunisation

Rhesus alloimmunisation occurs when a rhesus negative mother has an immunological response to a paternally derived rhesus D antigen, in a rhesus positive baby. The mother produces anti-D antibodies, which cross the placenta and cause haemolysis of the fetal D-antigen presenting erythrocytes leading to fetal anaemia (and subsequent fetal hydrops) [10,11]. The introduction of Rhesus D anti-sera in the 1970's has almost eliminated this once common cause of immune fetal hydrops in the West, but it remains a common cause of fetal hydrops in developing countries.

Alloimmunisation can occur to a number of other antigens on the surface of the fetal erythrocytes leading to hydrops or haemolytic disease of the newborn. The discussion of this is beyond the scope of this paper, but fully explained by Urbaniak and Griess (2000) [10].

4.1.2 Antiplatelet antibodies

All human platelets exhibit proteins on their surface called human platelet antigens (HPAs), which are bi-parentally inherited. On rare occasions a pregnant mother can develop antibodies to the unrecognised paternally derived HPAs, which leads to fetal platelet destruction and thrombocytopaenia [12]. The commonest antibody is HPA-1A seen in the context of the maternal haplotype HLA DRB3*0101 [13,14]. Severe fetal thrombocytopaenia can cause fetal haemorrhage, typically intracerebral, in the third trimester. Fetal haemorrhage can cause fetal hydrops by way of fetal anaemia [12,15,16].

4.2 Non-immune causes of fetal anaemia

4.2.1 Fetal haemorrhage

Fetal haemorrhage, whether internal (intracerebral or subdural) or feto-maternal, can lead to anaemia and therefore non-immune fetal hydrops [17]. Feto-maternal haemorrhage is the loss of fetal blood into the maternal circulation. Feto-maternal haemorrhages can occur in isolation or occur as chronic, slow bleeds.

Often there are minimal symptoms of a fetal haemorrhage but reported reduction in fetal movements should raise suspicion. An assessment for fetal anaemia should then be promptly undertaken. The Kleihauer-Betke smear performed on a maternal blood sample will identify the presence of fetal erythrocytes in many (but not all) cases of fetal maternal haemorrhage [18]. Imaging, such as fetal ultrasound or MRI, can be used for the assessment of internal fetal haemorrhage (the majority of which will be intracerebral). Fetal blood transfusion can improve or reverse the fetal hydrops but there may be proceeding neurological injury [19].

4.2.2 Infection

Erythema infectiosum (also known as fifth disease) is a common disease of childhood and mainly causes a mild flu-like illness with or without pruritus and erythematous malar rash (‘slapped cheek’). The condition is most frequently caused by contact with respiratory droplets infected with Parvovirus B19 (PB19), a single-stranded DNA virus. By reproductive age just over half of women are immune to PB19 [20,21]. However, an additional 1.5% of pregnant women seroconvert each year during endemic periods [22].

In approximately one quarter of cases the infection is vertically transmitted (transplacental) to the fetus, yet only a minority of those fetuses, biochemically proven to be infected, will

have an adverse outcome as a result [23]. Parvovirus has an affinity for erythroid progenitor cells leading to their infection and apoptosis [24]. This can result in fetal anaemia as evidenced by increased middle cerebral artery peak systolic velocity (MCA PSV), high output cardiac failure and subsequent fetal hydrops.

Parvovirus B19 infection accounts for approximately 4% of all cases of fetal hydrops (7.1% when the infection occurs between weeks 14 and 20 of pregnancy) [25]. Hydrops in these cases results from infection of erythroid progenitor cells, shortened erythroid cell life span and high output cardiac failure, aggravated by direct infection of cardiac myocytes leading to myocarditis [26]. In about one third of cases the fetal anaemia/fetal hydrops resolves spontaneously. Less frequently parvovirus B19 infection, particularly in the first half of a pregnancy, can lead to brain anomalies resulting in neurodevelopmental disorders [27]. The presence of fetal hydrops is the strongest predictor of fetal mortality in this group [28].

Other maternal infections that have been associated with fetal hydrops include Cytomegalovirus, Toxoplasma gondii, Treponema pallidum, herpes simplex virus (HSV) and Zika Virus [29–31]. The mechanism is thought to be anaemia, secondary to bone marrow infection, causing red cell aplasia, or direct effects of infection on cardiac myocytes leading to decreased cardiac efficiency [29]. Effects on bone marrow would be causative of hydrops in the third trimester when the fetal bone marrow becomes primarily responsible for red cell production.

There is good evidence that intra-uterine fetal blood transfusions can reverse fetal anaemia and improve outcomes in these cases [32,33].

4.2.3 Twin-Twin Transfusion

Twin-twin transfusion syndrome (TTTS) is a serious complication of 10-15% of monochorionic multiple pregnancies and is the most significant cause of death in twin pregnancies [34]. The condition arises due to presence of vascular anastomoses between vessels belonging to each fetus within a shared placenta. The reason why not all monochorionic multiple pregnancies develop TTTS is not clear.

The anastomoses can be arterial-arterial, vein-vein or arterial-venous and it is postulated that it is both the number and calibre of these anastomoses which determines severity. Where abnormal connections lead to unequal distribution of blood flow the 'recipient' twin can become polycythaemic, polyuric (leading to polyhydramnios) and hypertensive with fetal hydrops. The 'donor' twin is hypotensive, has poor growth and urine output with resulting oligohydramnios [35].

TTTS is staged using the Quintero system[36], which categorises cases by severity. Quintero stage one is the least severe with polyhydramnios only. In Stage two it is not possible to visualise the bladder of the donor fetus and is an indication for fetoscopic laser photocoagulation therapy. Quintero stage 3 describes flow abnormalities in the umbilical artery and vein on doppler ultrasound. Quintero stage four is defined by the presence of fetal hydrops [36]. Stage 5 indicates demise of one or more fetus. Laser photocoagulation therapy aims to divide the anastomoses and separate the fetal circulations. This significantly improves fetal survival, but approximately 10% of the surviving babies have adverse neurological outcomes [37].

4.2.4 Thalassaemia

Alpha thalassemia is caused by mutations in the alpha-globin genes leading to a reduction or absence of their product: alpha-globin. The normal adult state is to have two alpha-globin genes tandemly encoded (in cis) on each of an individual's two chromosome 16 (i.e. 4 alpha-globin genes in total). During the embryonic stage the alpha-like globin, sigma-globin, forms a tetramer with two epsilon-globin chains. During the 6th week of gestation, erythropoiesis becomes a primary function of the fetal liver (rather than yolk sac) and fetal haemoglobin consisting of two alpha and two gamma-globulin chains are produced [38]. If a baby inherits a chromosome 16 with the alpha-globin genes deleted or has a pathogenic mutation in both alpha chains (--/--) from each parent, haemoglobin tetramers assembled will consist entirely of beta chains. This results in Hb-Barts (homozygous alpha-thalassaemia), which normally results in fetal loss (anaemia, hypoxia and non-immune fetal hydrops) in the third trimester [39]. Rarely, HbH disease (--/-a) has been identified as a cause of fetal hydrops [40].

Most alpha-thalassaemias are deletional in genetic aetiology [41]. However, the severity of those alpha-thalassaemias caused by mutations is dependent on the extent to which the mutation causes reduction in protein product. A specific deletional mutation found in Southeast Asia (--^{SEA}) accounts for more than 90% of cases of non-immune fetal hydrops in this geographical region [42].

Beta-thalassaemia is caused by mutations in the *HBB* gene which encodes the haemoglobin B subunit that gradually replaces the gamma-globulin chains specific to fetal haemoglobin. As the shift to beta-globin subunits does not occur until post-natal life, HBB mutations are not a cause of fetal hydrops.

4.2.5 Congenital anaemias

4.2.5.1 Diamond-Blackfan Syndrome

Diamond-Blackfan Syndrome, first characterised in 1938, is a rare inherited bone marrow failure syndrome [43]. Mutations in 19 ribosome protein encoding genes have been implicated in this condition [44] as well as mutations in *GATA1* [45] and *TSR2* [46]. Complications include congenital structural abnormalities such as orofacial, hand, genitourinary and cardiac abnormalities (50% of cases), growth retardation (30% of cases) and predisposition to malignancy [47,48]. Skeletal manifestations are typically radial: triphalangeal, bifid or duplicated thumbs or radial hypoplasia [49]. Most cases present within the first year of life. Fetal hydrops is a poor prognostic indicator and results from severe intrauterine anaemia. It is a rare manifestation of Diamond-Blackfan, with fewer than 10 cases reported [50]. Specific truncating mutations in the ribosomal protein *RPL15* seem to confer the greatest risk of fetal hydrops [50]. First line treatment is with glucocorticoids with chronic blood transfusions and stem-cell transplants reserved for glucocorticosteroid non-responders. Cases presenting antenatally are treated with in-utero blood transfusions, first used in this condition in 1997 [49].

4.2.5.2 Congenital Dyserythropoietic Anaemia type 1

Congenital dyserythropoietic anaemia type 1 (CDA I) is another rare bone marrow failure syndrome. Complications include macrocytic anaemia, bony abnormalities and secondary haemochromatosis. Most cases are caused by mutations in *CDAN1* [51]. The product of *CDAN1*, codanin-1 is important for terminal erythrocyte differentiation, disruption of which leads to dyserythropoiesis [52]. So far fewer than ten cases of CDA I presenting as fetal

hydrops have been reported in the literature, only two of those had a molecular genetic diagnosis, both with mutations in *CDAN1* [52,53]. Intrauterine blood transfusions have been used as a bridge to postnatal allogenic bone marrow transplant with varying degrees of success. Additional genes have been implicated in CDA (types 2 and 3 and rarer variants) although these have been less frequently associated with fetal hydrops, and tend to have a milder phenotype.

4.2.5.3 Transient Abnormal Myelopoesis (TAM) in the context of Trisomy 21

Individuals with trisomy 21 (Down syndrome) are at increased risk of myeloproliferative disorders throughout life [54] . A transient, abnormal myelopoesis (TAM) is recognised to affect approximately 10-15% of infants with trisomy 21 [55]. The trisomy 21 is responsible for an initial dysmegakaryopoesis and, with an acquired *GATA1* truncating mutation, control of clonal proliferation of blasts cells is lost [56]. The result is a transient abnormal myelopoesis with up to 30% developing into myeloid leukaemia, by the age of 4 years, after acquisition of additional oncogenic driver mutations [57]. In a study by Tamblyn *et al*, of 31 cases of prenatally diagnosed TAM, 79.5% had hepatosplenomegaly and 30.8% had fetal hydrops. In the 33% of cases with both fetal hydrops and hepatomegaly the fetal or early neonatal mortality was 92% (54% with fetal hydrops alone) [58]. Thus fetal hydrops is a poor prognostic sign as the survival rate for postnatally detected cases is in the region of 70% with most babies undergoing spontaneous resolution of the abnormal myelopoiesis [55,59]. A recent report shows promising results for in-utero treatment with exchange transfusions and low dose cytarabine [60].

5 Non-anaemic with thoracic space occupying lesion on ultrasound

Detailed fetal ultrasound may identify a space occupying lesion causing *Impairment of lymphatic or venous drainage* (Figure 3).

5.1 Congenital Pulmonary Airway Malformation and Pulmonary Sequestrations

A congenital pulmonary airway malformation (CPAM) of the lung is a developmental abnormality caused by the failure of maturation of the bronchiolar structures during lung development. This results in overgrowth of terminal bronchioles without alveoli [61]. These are usually identified at the 20-week anomaly scan. CPAMs can be microcystic, macrocystic or a mixed type. In up to 65% of cases, the CPAM will spontaneously regress, possibly due to outgrowing of its blood supply [62]. In a large retrospective study of CPAM affected pregnancies, those cases without fetal hydrops had a 95% chance of survival. Those cases which developed hydrops, and were managed expectantly, had a 95% risk of perinatal death [63].

Pulmonary sequestrations (PS) are collections of non-functional lung tissue, which may or may not be cystic in nature but can be differentiated on fetal ultrasound from CPAM by identifying a systemic (rather than pulmonary) arterial supply [64,65]. PS can lead to the development of pleural effusions, non-immune fetal hydrops and perinatal death. The treatment of the pleural effusions with thoracentesis, thoracoamniotic shunts, intraperitoneal injection of frusemide/digoxin and laser coagulation leads to survival in the majority (91/95 in the case review by Cavoretto *et al*) but many will go on to need repeat procedures such as postnatal sequestrectomy due to pleural effusion reaccumulation [63].

5.2 Cardiac tumours

The three most common types of cardiac tumour in fetuses, newborns and children are rhabdomyomas (60%), teratomas (25%) and fibromas (12%) [66]. On ultrasound, rhabdomyomas often present in multiple as homogenous, hyperechogenic masses of varying sizes [66]. They are considered to be hamartomas as they are overgrowths of tissue that is normally present rather than being neoplastic [67]. The masses are usually located in the ventricles and septal walls but are occasionally found in the atria and pericardium. In one metanalysis by Chao *et al.* (2008) of fetuses with cardiac rhabdomyomas, 63.9% (85/133) were identified as having tuberous sclerosis complex and more than 80% of those with multiple rhabdomyomas. The authors also found that larger tumours increased the risk of developing haemodynamic compromise and rhythm disturbance and in turn the development of non-immune fetal hydrops and a high risk of fetal demise [68]. Recently, mTOR inhibitors such as sirolimus have been used for intra-uterine treatment but this remains a matter of debate given the potential maternal side effects[182,183].

Pericardial teratomas are germ-cell tumours found in the pericardium. They often cause significant pericardial effusions and mediastinal compression, which leads to reduced venous return and non-immune fetal hydrops. Whilst these tumours are rarely malignant and can be successfully treated postnatally, prognosis remains guarded. In fact, prognosis in this condition is more closely related to the development of the fetal hydrops than the malignant potential of the tumour [69]. Elective delivery, pericardiocentesis and thoracoamniotic shunting are the mainstays of in-utero teratoma therapy [70,71].

6 Non anaemic with cardiac abnormalities on ultrasound

Detailed fetal ultrasound may identify an abnormality of cardiac development as the primary cause (Figure 3). These include structural malformations, arrhythmias, cardiomyopathy or tumours.

6.1 Structural cardiac malformations

Abnormalities of cardiac development are a significant contributor to the total incidence of fetal hydrops. Some aetiological studies have determined that cardiac causes explain approximately 20% of all non-immune fetal hydrops [72]. Fetal cardiac echocardiography will identify many of these abnormalities and should be performed by a fetal cardiac specialist. Fetal echocardiography can be diagnostic from 13-14 weeks gestation. However, more subtle lesions may only become evident from 19-22 weeks gestation (e.g. ventricular septal defects). Screening of the fetal heart is generally integrated into the mid-trimester anomaly scan at 19-22 weeks gestational age.

Most structural abnormalities of the heart do not lead to hydrops due to presence of fetal shunts (foramen ovale and arterial duct) and low resistance to systemic arterial blood flow related to the placental circulation. Fetal hydrops develops in the presence of failure of both ventricles. See Table 1 for a detailed list of structural cardiac abnormalities causing fetal hydrops. In virtually all cases of hydrops related to a cardiac abnormality the heart is enlarged and the degree of enlargement has been shown to correlated with the central venous pressure [73]. Those babies with a congenital cardiac malformation who develop fetal hydrops have an extremely poor prognosis with a mortality rate of 92% [9]. A proportion of those babies with structural cardiac malformations will be identified as having causative chromosomal abnormalities or single gene disorders.

6.2 Arrhythmia

Fetal arrhythmias are detected in 2% of all pregnancies, which usually consist of isolated atrial ectopic beats [74]. Most fetuses with ectopic beats have an unremarkable course but a tachycardia may supervene in a small minority [75]. Tachycardias can lead to a low cardiac output state and non-immune fetal hydrops [74]. The most common types of tachycardia are supraventricular tachycardia (SVT) and atrial flutter. Ventricular tachycardia (VT), atrial fibrillation and chaotic atrial tachycardia are diagnosed rarely during fetal life. Fetal VT is most commonly torsades des pointes due to fetal long QT syndrome [76]. Where a fetus develops congestive cardiac failure secondary to arrhythmia there is an increased venous hydrostatic pressure leading to increased capillary permeability and shift of fluid into the interstitial spaces causing oedema. All tachycardias (HR>200180bpm) and bradycardias (HR<110bpm) can lead to non-immune fetal hydrops.

Supraventricular tachycardia, the most common cause of fetal tachycardia (~70%), is an important cause of non-immune fetal hydrops, not least because it is treatable [77]. In postnatal life most cases of SVT will not persist beyond the first year. Where there is significant fetal compromise, treatment consists of the transplacental administration of drugs such as digoxin, flecainide or sotalol.

Non-immune fetal hydrops can occur as a result of other tachyarrhythmias such as atrial flutter and rarely ventricular tachycardia.

Fetal bradyarrhythmias are less common and more difficult to treat. Sinus bradycardias are typically due to sinus node dysfunction, most commonly due to fetal long QT syndrome [78] or left atrial isomerism [78]. We have also seen fetal bradycardia causing hydrops due to the

autosomal recessive Jervell Lange-Nielson Syndrome caused by mutations in KCNQ1. Transient sinus bradycardia is frequently observed with probe pressure and resolves when this is removed. A subnormal ventricular rate can be due to multiple blocked atrial ectopic beats (typically resolve spontaneously) or 2nd or 3rd degree (complete) atrioventricular block. Complete heart block is most commonly due to maternal anti-Ro/anti–La antibodies or structural heart disease notably discordant AV atrioventricular connections or left atrial isomerism. Anti-Ro and anti-La antibodies can be transferred transplacentaly in mothers with systemic lupus erythematosus causing neonatal lupus and complete heart block in 2% of affected pregnancies [79]. Mothers carrying Anti-Ro and / or Anti -La antibodies who have had one fetus affected have an increased risk of 15-20% of subsequent pregnancies being affected by complete heart block. Treatment of immune mediated complete heart block is controversial. In selected cases dexamethasone, salbutamol or intravenous immunoglobulin are used, but without trial evidence of efficacy. Mothers known to carry Anti-Ro/La antibodies may be treated with hydroxychloroquine which might reduce the incidence of heart block[80]. Another important cause of persistent fetal bradycardia is atrioventricular conduction blocks in which the development of non-immune fetal hydrops is a poor prognostic sign.

6.3 Cardiomyopathies

Fetal cardiomyopathies are rare accounting for up to 11% of all fetal cardiac presentations [81]. The cardiomyopathies can be divided into dilated, where there is dilatation and reduced ventricular function of one or both ventricles and hypertrophic, where there is concentric ventricular or septal thickening [82].

6.3.1 Dilated cardiomyopathy

Dilated cardiomyopathy (with dilatation and reduced ventricular function of one or both ventricles) is rare in fetal life. Sivasankaran *et al.* reported on 50 cases of fetal dilated cardiomyopathy collected over a 20-year period in a specialist fetal cardiology clinic[83] [83]. Of those 50 cases, two-thirds developed hydrops at some point. Causes were varied including genetic (largely inborn errors of metabolism), anaemia, infection, and associated renal and cardiac abnormalities. Overall survival for those fetuses that developed hydrops was just 18% (compared to a 50% survival in the non-hydropic group) [83].

6.3.2Hypertrophic cardiomyopathy

Noonan syndrome (discussed in more detail in 'single-gene disorders' is associated with a prenatal onset of hypertrophic cardiomyopathy (HCM). There is some genotype-phenotype correlation with those individuals with mutations in *RAF1* developing cardiomyopathy in 56% of cases and those with mutations in *RIT1* in 75% of cases, compared to *PTPN11*-related cardiomyopathy in 9% of cases and *SOS1*-related cardiomyopathy in 10% [84]. The development of hypertrophic cardiomyopathy may not be evident until the third trimester so that serial fetal echocardiography is indicated for pregnancies at risk.

Barth Syndrome is an X-linked disorder of mitochondrial function and stability caused by mutations in *TAZ* [85]. Clinically the condition results in a dilated cardiomyopathy with endocardial fibroelastosis, which can lead to hydrops antenatally [86]. On fetal echocardiography, crypts are characteristically seen in the apex and free wall [82]. Those that survive may show growth retardation, proximal skeletal myopathy, neutropenia and organic aciduria [85,87].

Hypertrophic cardiomyopathy has been associated with other inborn errors of metabolism. 63% of patients with congenital disorders of glycosylation have been shown to develop HCM, although this is based in relatively small numbers [88].

6.4 High-output cardiac failure

The majority of hydrops cases with high output cardiac failure will result from fetal anaemia, but here we detail some of the additional causes of fetal high-output cardiac states.

6.4.1 High flow Arteriovenous Malformations

Arteriovenous malformations (AVMs) cause fetal hydrops secondary to high output cardiac failure. Vascular malformations are typically seen in the lungs as pulmonary arteriovenous malformations [89]. In the brain both cerebral arteriovenous malformations and vein of Galen aneurysms leading to fetal hydrops[90,91] Hydrops is also reported in cases with large congenital cutaneous haemangiomas[92].

6.4.2 Sacrococcygeal teratomas

Sacrococcygeal teratomas (SCTs) affect approximately 1 in 27,000 births [93]. SCTs appear as mixed echogenicity masses, which extend from the fetal sacrum, and those which grow rapidly and are highly vascular are associated with increased mortality [94]. The high vascularity can lead to high output cardiac failure and subsequent fetal hydrops. The development of fetal hydrops leads to a 3.4-fold increase in SCT related mortality [95]. When the fetus is noted to be in a high-output cardiac state, and at risk of developing hydrops, fetal therapy can be considered consisting of open fetal surgical debulking, shunt placement or radiofrequency ablation [94][82].

6.4.3 Thyroid abnormalities

It is well established that the use of antithyroid drugs can lead to congenital malformations. Shveiky (2004) reports a case of late-onset fetal hydrops in a woman taking propylthiouracil for Grave's disease [96]. It is postulated that the non-immune fetal hydrops resulted from a high-output cardiac failure due to an arterio-venous shunt in the large fetal goitre present. Interestingly in the case, levothyroxine was administered into the amniotic fluid (200μg per week for three weeks), which led to regression of the fetal hydrops and a reduction in the size of the fetal goitre, thus mitigating any potential peripartum dystocia or neonatal airway issues [96]. Additionally, exposure to maternal circulating autoantibodies to TSH receptors (Grave's disease) can lead to fetal hyperthyroidism with fetal tachycardia, highly vascular goitre and cardiac failure resulting in fetal hydrops [97,98].

7. Non anaemic, with no primary space occupying or cardiac abnormality

If cardiac developmental abnormality has been excluded as the primary cause, then there are several other underlying reasons for the fetal hydrops that can be considered, such as chromosome abnormalities, single gene disorders, gastrointestinal or urogenital malformations (Figure 3).

7.1 Chromosome abnormalities

Chromosome aneuploidies are frequently seen in the fetus with raised nuchal translucency. This may progress to fetal hydrops. Trisomy 21 (Down syndrome) affects 13 in 10,000 live births (data from the USA) [99]. Not all cases of Down syndrome develop fetal hydrops, which likely results from aberrant lymphatic development [100]. Other features of Down syndrome may be seen prenatally including duodenal atresia, sandal gap, absent nasal bone

and cardiac anomalies (e.g. endocardial cushion defects and septal wall defects). In the third trimester some babies with Down syndrome develop fetal hydrops as a result of a transient myeloproliferative disorder and associated anaemia as described [101].

Trisomy 18 (Edward Syndrome) and Trisomy 13 (Patau Syndrome) are also relatively frequently diagnosed in the context of fetal hydrops. Both are multisystem disorders with Edward syndrome characteristically recognised by the ultrasound demonstration of clenched hands and 'rocker-bottom feet'. Midline defects are prominent in Patau syndrome with holoprosencephaly and cyclopia seen in addition to multisystem abnormalities. Fetal hydrops develops in 14% of fetuses with trisomy 18 and 3% of those with trisomy 13 [102].

Turner syndrome (45X0) is the commonest cause of genetic fetal hydrops [103]. Aside from significantly raised nuchal translucency and hydrops, renal malformations and congenital cardiac disease (most commonly coarctations of the aorta) are seen. In postnatal life individuals may have dysmorphism, short stature with mild learning difficulties and congenital four-limb lymphoedema which resolves during childhood (but may return) [104]. The presence of fetal hydrops in patients with Turner syndrome is a poor prognostic indicator within the region of 80-99% of affected fetuses suffering in-utero demise [105,106].

It is not unusual to find more complicated karyotype abnormalities in the context of non-immune fetal hydrops. This can include duplications, deletions, insertions and inversions some of which cause well recognised post-natal syndromes such as Pallister-Kilian syndrome (mosaic tetrasomy 12p) and Di George syndrome (22q11 microdeletion) [107,108].

The gold-standard for the diagnosis of fetal chromosome abnormalities is through invasive testing (amniocentesis or chorionic villus sampling). Most women with a pregnancy with trisomy 21 are identified as having a high-risk pregnancy based on first trimester screening, which combines the measurement of the fetal nuchal translucency with the maternal serum markers (Papp-A, free-beta HCG) [109].

Increasingly women are being tested using NIPT (Non-Invasive Prenatal Testing). From a simple maternal blood sample, a new highly sensitive and specific screening test can quantify fetal chromosome 21 fragments freely circulating in the maternal blood [110]. The test is also proving to be increasingly accurate for trisomies 13 and 18 and is now offered for other chromosome deletion syndromes (with significantly reduced sensitivity and specificity) [111].

7.2 Single Gene disorders

The single-gene disorders associated with fetal hydrops can be divided into inborn errors of metabolism, haematological disorders, lymphatic disorders (including RASopathies), skeletal dysplasias, and a miscellaneous group. The pathogenesis of the hydrops in this group of multiple abnormality syndromes can be multi-factorial with cardiac, lymphatic and haematological abnormalities all contributory within the same single-gene disorder.

It is important to recognise that almost any single-gene disorder, which presents with a severe phenotype *in-utero,* has been or may be identified as causing non-immune fetal hydrops. This is less the product of the specific genetic aberration but more due to the recognition that fetal hydrops is routinely observed in the decompensating fetus. This is

likely due to a vicious cycle of cardiac dysfunction, poor perfusion and imbalanced fluid homeostasis and portends an ominous prognosis.

7.2.1 Lymphatic abnormalities

Primary lymphatic anomalies may be caused by mutations in a number of genes [112]. Many of these disorders have been seen presenting antenatally with fetal hydrops. In addition, there is a group of syndromes (RASopathies and PIK3CA-related overgrowth syndromes) that have been grouped here owing to the associated fetal hydrops resulting from lymphatic malformation.

Homozygous mutations in *PIEZO1* cause generalised lymphatic dysplasia of Fotiou in postnatal life and can present prenatally as non-immune fetal hydrops [113]. The *PIEZO1* gene encodes a highly conserved, large transmembrane protein that is a mechanically activated cation channel [114]. Postnatally affected individuals, in addition to widespread lymphoedema, may have systemic complications including pulmonary lymphangiectasia, pleural effusions chylothoraces and pericardial effusions [104]. Autosomal dominant gain-of-function mutations in *PIEZO1* cause dehydrating hereditary stematocytosis which can also present with a severe fetal hydrops/ perinatal oedema phenotype[110]

Heterozygous mutations in *EPHB4* have been shown to cause non-immune fetal hydrops and with extensive fetal morbidity [115]. EPHB4 binds to Ephrin B2, a transmembrane protein, inducing a signalling cascade essential for the development of lymphatic vessel and valve formation during embryonic and neonatal life [115–117]. Survivors may develop lymphoedema and or varicose veins later in life [115].

Hennekam syndrome was first described in 1989 in a series of related individuals with severe limb, genital and facial lymphoedema as well as poor growth, seizures and intellectual impairment [118]. One type of Hennekam syndrome is caused by pathogenic mutations in *CCBE1* [119]. CCBE1 is crucial to lymphangiogenesis due to its role in lymphangioblast budding [120], and mutations have been shown to cause recurrent fetal hydrops [121,122]. Mutations in *FAT4*, *ADAMTS3* and *FBXL7* have also been implicated Hennekam Syndrome [123–125].

Heterozygous mutations in the gene *FLT4 (VEGFR3)* cause Milroy disease, which typically presents at birth, or soon after, with bilateral pedal oedema [126]. There have been rare reports of antenatal presentation of *FLT4/VEGFR3* mutations, including fetuses affected by ascites, pleural effusions and limb oedema [127–129].

Lymphoedema-distichiasis is caused by pathogenic mutations in the forkhead transcription factor gene *FOXC2* [16]. The syndrome is characterised by pubertal onset of lower limb lymphoedema and additional congenital abnormalities, namely distichiasis (aberrant growth of eyelashes). Other malformations are observed including varicose veins, cardiac defects, cleft palate, ptosis and spinal extradural cysts [130]. Cases of non-immune fetal hydrops with *FOXC2* mutations are reported, but it is not a primary feature of the condition suggesting that affected cases may have genetic modifiers, which worsen the severity of the presentation [16,131,132].

7.2.2 The RASopathies

The RASopathies are a group of disorders caused by germline mutations in crucial elements of the RAS/mitogen-activated protein kinase (MAPK) pathway, which controls cell

differentiation, proliferation and survival [133]. There is much phenotypic overlap in these disorders with most having variations on a recognisable pattern of facial dysmorphism, short stature and congenital heart disease.

The RAS-MAPK pathway disorders are an important group to consider in relation to fetal hydrops, as they are recognised to present antenatally with raised nuchal translucency, hydrothorax or non-immune fetal hydrops as a result of aberrant lymphatic development [134].

In Noonan syndrome, approximately 50% of cases who present postnatally are found to have mutations in *PTPN11* [135,136]. As we carry out increasing amounts of in-utero genetic sequencing, we may find that antenatal presentation correlates more strongly with a different Noonan-causing gene. It is reported that 59% of pregnancies affected by Noonan Syndrome show a consistent pattern of raised nuchal translucency, pleural effusions and non-immune fetal hydrops, as well as polyhydramnios and cardiac defects [137]. Absence of the ductus venosus has also been observed in approximately 50% of cases [137,138]. It is thought that the lymphatic abnormalities in fetuses with Noonan syndrome result from a disturbance in lymphatic endothelial differentiation due to diminished expression of the lymphatic markers PROX1 and Podoplanin and an increase in the vascular markers VEGF-A and Neuopilin-1 [139]. The fetal hydrops in Noonan syndrome is likely due to lymphatic malformation rather than congenital heart disease.

There is some evidence of genotype-phenotype correlation within Noonan syndrome. Patients with *RIT1* mutations have a much higher incidence of hypertrophic cardiomyopathy (see 'cardiomyopathies') (54%) but also perinatal abnormalities (100%), including raised nuchal translucency (67%), polyhydramnios (67%), fetal hydrops (38%), and pleural

effusions (62%) [84]. The diagnosis of Noonan syndrome during pregnancy can be enormously helpful. A persistently raised nuchal translucency is a strong predictor of Noonan syndrome[138] and is seen in postnatal life as the neck webbing typical of this condition. If the fetus does not develop significant cardiac compromise, these babies often survive and can go on to lead healthy lives, sometimes with minimal intellectual deficit.

7.2.3 Inborn errors of metabolism (IEM)

7.2.3.1 Lysosomal Storage disease (LSD)

Most babies with IEM-related hydrops will have a lysosomal storage disease (LSD), 17 of which have been shown to cause non-immune fetal hydrops to date [140]. In a systematic review by Gimovsky *et al.* (2015), in 678 cases of non-immune fetal hydrops, 5.2% were diagnosed with an LSD during the pregnancy. Of those cases labelled as 'idiopathic', 17.4% were later diagnosed with an LSD on post-natal investigations [141]. Mucopolysaccharidosis type VII represented 20% of all LSD diagnoses, Gaucher was the next most frequent at 17.1%, followed by GM1-gangliosidosis at 14.3% [141].

The non-immune fetal hydrops resulting from LSDs typically starts in the second trimester and may be associated with hepatosplenomegaly and ascites [142]. It is postulated that the fluid is accumulated due to venous obstruction secondary to visceromegaly resulting from abnormal accumulation of storage material [143].

7.2.3.2 Other Metabolic disorders

The peroxisomal biosynthesis disorders, are an umbrella term for a spectrum of disorders ranging from the severe Zellweger syndrome, intermediate neonatal adrenoleukodystrophy

and mild Infantile Refsum disease [144]. These are recessively inherited disorders caused by mutations in the *PEX* genes, and there are rare reports of antenatal hydrops presentation in addition to varied, non-specific, dysmorphism [140,145].

Smith-Lemli-Opitz (SLO) is a recessively inherited multiple malformation syndrome caused by mutations in DHCR7 leading to deficiency of 7dehydrocholesterol reductase [146]. Fetal hydrops has been reported, possibly related to fetal akinesia (and lymphatic stasis) [147,148]. Individuals with SLO typically have microcephaly, characteristic facial dysmorphism, polydactyly, intellectual disability and autistic spectrum disorder [146,149].

Other inborn errors of metabolism associated with non-immune fetal hydrops include glycogenosis type IV, transaldolase deficiency, congenital disorders of glycosylation and citric acid cycle defects [88].

7.2.3.3 Prenatal diagnosis in suspected metabolic disorder

Differentiating between inborn errors of metabolism on ultrasound and history alone is very challenging (although hepatosplenomegaly is a clue to LSDs). In recent clinical practise, we are able to undertake large gene panel or clinical exome sequencing (coding parts of DNA in a pre-determined 'virtual' panel of genes) in cases of suspected metabolic disorder. Exome testing may identify mutations in any of a large panel of genes associated with IEM related hydrops. Often, the knowledge of the metabolic diagnosis during the pregnancy allows for better prognostication and subsequent informed decision making regarding the pregnancy. In those babies, which survive to term and beyond, a diagnosis can prevent the need for a series of invasive, time-consuming and expensive diagnostic procedures in the neonatal period.

Sundrie-Arnaud *et al.* undertook a study of 46 cases with non-immune fetal hydrops, polyhydramnios associated with additional fetal anomaly or effusions for whom no explanation had been identified (via autopsy and standard genetic testing) [140]. DNA from all cases underwent Next Generation Sequencing (NGS) using a panel of 41 IEM genes. A causative mutation in a gene associated with IEM was found in 6 (13%) of cases [140].

7.2.4 Skeletal Dysplasias

There are more than 450 skeletal dysplasias described in the literature [150]. Many of these can be diagnosed antenatally by ultrasound identification of short long bones, abnormal bone morphology, abnormal bony opacity (aberrant mineralisation) or additional or missing bones for that gestational age. The specific diagnosis can be particularly challenging prenatally and effort is made to differentiate those skeletal dysplasias, which are lethal from those which are not. This is information that is particularly useful to parents when making decisions about managing a pregnancy. Consideration must also be given to delivery as many skeletal dysplasia are complicated by fractures and the incidence of traumatic birth can be reduced with the decision to undertake a planned caesarean section.

The prenatal ultrasound is usually the first indicator of skeletal dysplasia. The earlier in a pregnancy that short femurs (>2 SD below mean for gestational age) are identified the more likely that the skeletal dysplasia will be of a lethal type [151]. An estimation of lung volume is essential as lethality arise from pulmonary hypoplasia resulting in inadequate pulmonary surface area for effective respiratory exchange [152]. Other features predicative of a lethal

skeletal dysplasia are: decreased femur length to abdominal circumference ratio, visceral abnormalities, severe polyhydramnios and fetal hydrops [153].

Ultrasound examination alone is often sufficient to determine lethality, but will not provide a specific diagnosis in about a third of all cases [154]. Improvements in genetic technology have allowed an accurate molecular diagnosis of the specific type of skeletal dysplasia [155]. Where there are well delineated genotype-phenotype correlations knowledge of the specific mutation can provide useful information about the natural history of the disorder [156]. There is now the option to undertake highly accurate molecular diagnosis from free-fetal DNA (Non-Invasive Prenatal Diagnosis/NIPD) for mutations in *FGFR3* [157] (accounting for some of the most frequently occurring skeletal dysplasias).

Many of the severe skeletal dysplasias seen antenatally are complicated by hydrops. The pathophysiology is not entirely clear. The development of non-immune fetal hydrops is likely secondary as a combination of different factors, including ineffective bony erythropoiesis (anaemia) and increased thoracic pressure causing lymphatic stasis [158].

7.2.5 Other single gene syndromic causes.

In postnatal life mutations in *FOXP3* cause an X-linked immune dysregulation, polyendocrinopathy, enteropathy and autoimmunity (IPEX) syndrome. The FOXP3 protein plays a critical role in T Regulatory cell production and function and essentially affected patients have dysfunction of their T_H1 lymphocytes [159] Whilst it is not a common cause of fetal hydrops there are multiple reports of hydrops in affected male fetuses[160,161]. Why the phenotype is so severe as to cause fetal hydrops in these cases remains unknown and the pathogenesis of the fetal hydrops is unclear.

Kabuki Syndrome is a well-recognised multiple malformation syndrome characterised by intellectual impairment, facial dysmorphism, short stature, persistent fetal finger pads as well as cardiac, vertebral and renal malformations [162]. Mutations in *KMT2D* cause autosomal dominant Kabuki syndrome, but it is becoming clear that there is an emerging phenotype, distinct from classical Kabuki, that has a more severe fetal presentation [163,164]. It is not a common cause of fetal hydrops.

7.3 Gastrointestinal malformation

Gastrointestinal causes are included in most aetiology reports of non-immune fetal hydrops. However, they make up a small percentage of all cases and there are a limited number of case reports. Meconium peritonitis results from the rupture of the fetal bowel and the leak of meconium into the peritoneal space. The inflammation that ensues appears as calcifications on the fetal ultrasound and dilated bowel loops. It is seen more frequently in fetuses with cystic fibrosis although it is still a rare complication. Meconium peritonitis usually causes ascites, but this has been shown to cause a more severe presentation of

hydrops [165]. Any cause of bowel infarction and resultant fluid loss into the peritoneal cavity (stenosis, atresia, volvulus, peritoneal bands, imperforate anus, intussusception) can cause oedema as a result of the reduced vascular colloid osmotic pressure [9].

7.4 Urogenital malformation

Urorectal septum malformation sequence (URSMS) leading to meconium peritonitis and non-immune fetal hydrops was first reported in 2006 [166]. Subsequently multiple papers looking at the aetiology of all fetal hydrops cases attribute a small percentage (2-3%) to 'urogenital malformations', including prune-belly syndrome, renal agenesis, neonatal Bartter syndrome and cystic kidney disease [2,72,167–169]. Still, non-immune fetal hydrops is an unusual presentation of urogenital tract malformations. There is little published in the literature which explores the relationship between urogenital malformations and fetal hydrops, or which attempts to explain the pathophysiology of the oedema.

7.5 Gestational Autoimmune Liver Disease/Neonatal hemochromatosis

Gestational autoimmune liver disease (GALD) occurs when there is transplacental passage of maternal IgG antibodies to fetal liver antigens[170, 178]. The ensuing destruction of fetal hepatocytes leads to fetal liver failure with fibrosis and cirrhosis. As in post-natal liver failure, there is fetal hypoalbuminaemia [171], which is likely to cause reduce vascular colloid osmotic pressure and fluid shift into the interstitium. Diagnosis is confirmed by identification of non-hepatic siderosis. Antenatal therapy with high dose IVIG (Intravenous Immune Globulin) has been shown to prove outcomes in pregnancies at risk of GALD [172].

7.5 Idiopathic

The 'idiopathic' group consists of cases where no cause for the fetal hydrops has been identified. In one recent multi-center study in the USA, 46% of cases of non-immune fetal hydrops remained undiagnosed after standard karyotype/chromosomal microarray plus exome analysis, with a further 9% with a suspected, but unconfirmed diagnoses [103]. A meta-analysis by Bellini's group in 2015, reported a lower 'idiopathic' diagnosis rate in a large cohort (18.2%), although there was no standardisation of genetic testing of the assignation of 'idiopathic' among the 24 papers included in the metanalysis [158].

As prenatal exome sequencing becomes increasingly available and with further gene discovery, we expect the percentage of undiagnosed cases to reduce. We believe that a large portion of the idiopathic group will be found to have mutations in genes (known or unknown) associated with normal lymphatic development or inborn errors of metabolism.

8. Ballantyne Syndrome and Maternal Oedema

In rare cases fetal hydrops can progress to oedema of the placenta and maternal oedema. This triad of symptoms has been coined Mirror syndrome (as it 'mirrors' the fetal state) and has been eponymously named after John William Ballantyne who first described the condition in 1892[173]. The exact incidence of this condition is unknown but it has been estimated to affect approximately 1 in 3000 pregnancies, although it is likely underdiagnosed[174,175]. One systematic review of 2010 found 56 case reports in the published literature and of those, maternal hypertension was present in 57-78% of cases, proteinuria in 20-56% with in-utero fetal death occurring in 56% of cases[176]. Fetal survival appears to be improved by correction of fetal anaemia and induction of labour[177]. It is

important to recognise Ballantyne syndrome as a differential diagnosis for preeclampsia as maternal oedema, hypertension, rapid weight gain, dyspnoea and albuminaemia characterise both conditions[175]. Ballantyne syndrome can be differentiated by the presence of a dilutional anaemia with a low maternal haematocrit[178].

9. Conclusions

Making a diagnosis in cases of fetal hydrops is pivotal to providing the parents with accurate information about the prognosis, both in the context of the pregnancy and in post-natal life, and recurrence risk. In the first trimester fetal hydrops is almost always associated with lethal chromosome abnormalities. From the second trimester the presence or absence of fetal anaemia can guide the clinician's investigatory pathway as outlined in Figure 3. Ultrasound imaging findings can identify thoracic space occupying lesions that cause a mechanical lymphatic obstruction or evidence of cardiac or vascular structural abnormalities, which cause hydrops secondary to increased cardiac work. Where fetal anaemia and cardiothoracic abnormalities have been excluded, single-gene disorders are the largest remaining group. Ultrasound features can be highly suggestive of specific single-gene disorders (especially skeletal dysplasias and metabolic disorders). Genetic sequencing via whole exomes will improve our diagnostic yield in these disorders but a significant proportion will remain undiagnosed.

Expert Opinion

The identification of non-immune fetal hydrops is a poor prognostic factor in a pregnancy and often indicates a decompensating fetus. Due to the multitude of potential causes

investigations must be prioritised based on ultrasound features and clues to underlying pathophysiology.

We have been in a position to provide a limited clinical exome sequencing service to these patients and have found that families find it helpful to have a molecular diagnosis when making difficult decisions about management of an affected pregnancy. We have found the diagnostic yield to be particularly high in cases of fetal abnormality with the addition of fetal hydrops (as yet unpublished data). In one case we have also been able to put in place early neonatal enzyme replacement therapy due to having made an accurate in-utero diagnosis.

In the future, as genetic sequencing becomes more routine, owing to increased affordability and rapid turn-around times, genetic testing will feature more prominently and earlier in the investigation process. It is foreseeable that, in the not too distant future, genomic testing will be undertaken from maternal blood as early as 9 weeks gestation, which will look not only for single gene disorders but also chromosome aneuploidies and copy number variants. Prenatal exome sequencing can now be undertaken in a matter of a few weeks and we expect turn-around times to continue to reduce, making this a primary investigation in cases of fetal hydrops.

However, further research is needed to identify casual genes. In the process of this research we will also expand the phenotype of genes, which cause well described postnatal phenotypes, into the prenatal setting. There are significant challenges to variant interpretation as assigning pathogenicity to a newly discovered variant is particularly complex in the context of the minimal phenotypic information available from in-utero investigations.

An early genetic diagnosis is valuable as it ends the 'diagnostic odyssey' thus preventing the need for continued invasive investigations throughout the rest of the pregnancy and post-natal life [80]. The next decade will dawn the era of precision medicine whereby a molecular diagnosis in cases of fetal hydrops will allow for the development and application of personalised therapeutics.

Funding

Dr Esther Dempsey is supported by the British Heart Foundation (FS/18/78/33932).

Declaration of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Acknowledgments

Prof. John Simpson acknowledges support by the Department of Health through the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's and St Thomas' National Health Service Foundation Trust in partnership with King's College London and King's College Hospital National Health Service Foundation Trust.

References:

[1] HEINONEN S, RYYNÄNEN M, KIRKINEN P. Etiology and outcome of second trimester non-immunologic fetal hydrops. Acta Obstet Gyn Scan. 2000;79:15–18.

[2] Derderian CS, Jeanty C, Fleck SR, et al. The many faces of hydrops. J Pediatr Surg. 2015;50:50–54.

[3] Fukushima K, Morokuma S, Fujita Y, et al. Short-term and long-term outcomes of 214 cases of non-immune hydrops fetalis. Early Hum Dev. 2011;87:571–575.

[4] Levick J. Circulation of fluid between plasma, interstitium and lymph.11 :188–219. In: An Introduction to Cardiovascular Physiology. 5th Edition. 2010 Hodder Arnold. London

[5] Randenberg A. Nonimmune Hydrops Fetalis Part I: Etiology and Pathophysiology. Neonatal Netw. 2010;29:281-295(15).

[6] Levick RJ, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res. 2010;87:198–210.

[7] Hellmund A, Berg C, Geipel A, et al. Prenatal diagnosis of fetal akinesia deformation sequence (FADS): a study of 79 consecutive cases. Arch Gynecol Obstet. 2016;294:697–707.

[8] Norton ME, Chauhan SP, et al. Society for Maternal-Fetal Medicine (SMFM) Clinical

Guideline #7: nonimmune hydrops fetalis. Am J Obstet Gynecol. 2014;212:127–139.

[9] Désilets V, Bie I, Audibert F. No. 363-Investigation and Management of Non-immune Fetal Hydrops. J Obstetrics Gynaecol Can. 2018;40:1077–1090.

[10] Urbaniak SJ, Greiss MA. RhD haemolytic disease of the fetus and the newborn. Blood Rev. 2000;14:44–61.

[11] Fung K, Eason E, Crane J, et al. Prevention Of RH Alloimmunization This guideline has been reviewed by the Maternal-Fetal Medicine Committee and the Genetics Committee, with input from the Rh Program of Nova Scotia, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada. J Obstetrics Gynaecol Can. 2003;25:765–773.

[12] Regan F, Lees C, Jones B, et al. Prenatal Management of Pregnancies at Risk of Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT). Bjog Int J Obstetrics Gynaecol. 2019;126:e173–e185.

[13] Kjær M, Bertrand G, Bakchoul T, et al. Maternal HPA-1a antibody level and its role in predicting the severity of Fetal/Neonatal Alloimmune Thrombocytopenia: a systematic review. Vox Sang. 2019;114:79–94.

[14] Kamphuis M, Paridaans N, Porcelijn L, et al. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. Bjog Int J Obstetrics Gynaecol.

2010;117:1335–1343.

[15] Jain V, Clarke G, Russell L, et al. A Case of Alloimmune Thrombocytopenia, Hemorrhagic Anemia-Induced Fetal Hydrops, Maternal Mirror Syndrome, and Human Chorionic Gonadotropin–Induced Thyrotoxicosis. Am J Perinatology Reports. 2013;03:041–044.

[16] Fang J, Dagenais SL, Erickson RP, et al. Mutations in FOXC2 (MFH-1), a Forkhead Family Transcription Factor, Are Responsible for the Hereditary Lymphedema-Distichiasis Syndrome. Am J Hum Genetics. 2000;67:1382–1388.

[17] Wylie BJ, D'Alton ME. Fetomaternal Hemorrhage. Obstetrics Gynecol. 2010;115:1039–1051.

[18] Kleihauer E, Braun H, Betke K. Demonstration von fetalem Hämoglobin in den Erythrocyten eines Blutausstrichs. Klin Wochenschr. 1957;35:637–638.

[19] Rubod C, Houfflin V, Belot F, et al. Successful in utero Treatment of Chronic and Massive Fetomaternal Hemorrhage with Fetal Hydrops. Fetal Diagn Ther. 2006;21:410–413.

[20] Enders G, Biber M. Parvovirus B19 infections in pregnancy. Behr Inst Mitt. 1990;74–78.

[21] Jensen I, Thorsen P, Jeune B, et al. An epidemic of parvovirus B19 in a population of 3596 pregnant women: a study of sociodemographic and medical risk factors. Bjog Int J Obstetrics Gynaecol. 2000;107:637–643.

[22] Valeur-Jensen A, Pedersen CB, Westergaard T, et al. Risk Factors for Parvovirus B19 Infection in Pregnancy. Jama. 1999;281:1099–1105.

[23] Yageashi N, Niinuma T, Chisaka H, et al. The incidence of, and factors leading to, parvovirus B19-related hydrops fetalis following maternal infection; report of 10 cases and meta-analysis. J Infection. 1998;37:28–35.

[24] Chisaka H, Morita E, Yaegashi N, et al. Parvovirus B19 and the pathogenesis of anaemia. Rev Med Virol. 2003;13:347–359.

[25] de Jong E, Walther F, Kroes A, et al. Parvovirus B19 infection in pregnancy: new insights and management. Prenatal Diag. 2011;31:419–425.

[26] Giorgio E, Oronzo M, Iozza I, et al. Parvovirus B19 during pregnancy: a review. J Prenat Medicine. 2010;4:63–66.

[27] Ornoy A, Ergaz Z. Parvovirus B19 infection during pregnancy and risks to the fetus. Birth Defects Res. 2017;109:311–323.

[28] Xiong Y, Tan J, Liu Y, et al. The risk of maternal parvovirus B19 infection during pregnancy on fetal loss and fetal hydrops: a systematic review and meta-analysis. J Clin Virol. 2019;114:12–20.

[29] Barron SD, Pass RF. Infectious causes of hydrops fetalis. Semin Perinatol. 1995;19:493–501.

[30] Sarno M, Sacramento GA, Khouri R, et al. Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. Plos Neglect Trop D. 2016;10:e0004517.

[31] Fuchs F, Michaux K, Rousseau C, et al. Syphilis Infection: An Uncommon Etiology of Infectious Nonimmune Fetal Hydrops with Anemia. Fetal Diagn Ther. 2016;39:74–77.

[32] Schild R, Bald R, Plath H, et al. Intrauterine management of fetal parvovirus B19 infection. Ultrasound Obst Gyn. 1999;13:161–166.

[33] Enders M, Weidner A, Zoellner I, et al. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. Prenatal Diag. 2004;24:513–518.

[34] Bamberg C, Hecher K. Update on twin-to-twin transfusion syndrome. Best Pract Res Cl Ob. 2019;

[35] Kontopoulos E, Chmait RH, Quintero RA. Twin-to-Twin Transfusion Syndrome: Definition, Staging, and Ultrasound Assessment. Twin Res Hum Genet. 2016;19:175–183.

[36] Quintero RA, Morales WJ, Allen MH, et al. Staging of Twin-Twin Transfusion Syndrome.

J Perinatol. 1999;19:7200292.

[37] Rossi CA, Vanderbilt D, Chmait RH. Neurodevelopmental Outcomes After Laser Therapy for Twin–Twin Transfusion Syndrome. Obstetrics Gynecol. 2011;118:1145–1150.

[38] Arcasoy MO, Gallagher PG. Hematologic disorders and nonimmune hydrops fetalis. Semin Perinatol. 1995;19:502–515.

[39] Chui D, Waye J. Hydrops fetalis caused by alpha-thalassemia: an emerging health care problem. Blood. 1998;91:2213–2222.

[40] Chan V, Chan T, Liang S, et al. Hydrops fetalis due to an unusual form of Hb H disease. Blood. 1985;66:224–228.

[41] Bernini LF, Harteveld CL. 2 α-Thalassaemia. Baillière's Clin Haematol. 1998;11:53–90.

[42] Clark B, Thein S. Molecular diagnosis of haemoglobin disorders. Clin Laboratory Haematol. 2004;26:159–176.

[43] Diamond L, Blackfan K. Hypoplastic anaemia. Am J Dis Children. 1938; 56;464-467.

[44] Aspesi A, Betti M, Sculco M, et al. A functional assay for the clinical annotation of genetic variants of uncertain significance in Diamond–Blackfan anemia. Hum Mutat. 2018;39:1102–1111.

[45] Sankaran VG, Ghazvinian R, Do R, et al. Exome sequencing identifies GATA1 mutations resulting in Diamond-Blackfan anemia. J Clin Invest. 2012;122:2439–2443.

[46] Gripp KW, Curry C, Olney A, et al. Diamond–Blackfan anemia with mandibulofacial dystostosis is heterogeneous, including the novel DBA genes TSR2 and RPS28. Am J Med Genet A. 2014;164:2240–2249.

[47] Vlachos A, Blanc L, Lipton JM. Diamond Blackfan anemia: a model for the translational approach to understanding human disease. Expert Rev Hematol. 2014;7:359–372.

[48] Noel C. Diamond–Blackfan anemia RPL35A: a case report. J Medical Case Reports. 2019;13:185.

[49] Mclennan Ac, Chitty Ls, Rissik J, et al. Prenatal diagnosis of Blackfan–Diamond syndrome: case report and review of the literature. Prenatal Diag. 1996;16:349–353.

[50] Wlodarski MW, Costa L, O'Donohue M-F, et al. Recurring mutations in RPL15 are linked to hydrops fetalis and treatment independence in Diamond-Blackfan anemia. Haematologica. 2018;103:haematol.2017.177980.

[51] Tamary H, Dgany O, Proust A, et al. Clinical and molecular variability in congenital dyserythropoietic anaemia type I. Brit J Haematol. 2005;130:628–634.

[52] Liu S, Liu Y-N, Zhen L, et al. Fetal-onset congenital dyserythropoietic anemia type 1 due to CDAN1 mutations presenting as hydrops fetalis. Pediatr Hemat Oncol. 2019;35:447–450.

[53] Chin H-L, Lee L, Koh P. Fetal-onset Congenital Dyserythropoietic Anemia Type 1 due to a Novel Mutation With Severe Iron Overload and Severe Cholestatic Liver Disease. J Pediatric Hematology Oncol. 2017;41:e51–e53.

[54] Hasle H, Clemmensen I, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet. 2000;355:165–169.

[55] Bhatnagar N, Nizery L, Tunstall O, et al. Transient Abnormal Myelopoiesis and AML in Down Syndrome: an Update. Curr Hematol Malig R. 2016;11:333–341.

[56] Wechsler J, Greene M, vitt MA, et al. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. Nat Genet. 2002;32:148–152.

[57] Nikolaev SI, Santoni F, Vannier A, et al. Exome sequencing identifies putative drivers of progression of transient myeloproliferative disorder to AMKL in infants with Down syndrome. Blood. 2013;122:554–561.

[58] Tamblyn J, Norton A, Spurgeon L, et al. Prenatal therapy in transient abnormal myelopoiesis: a systematic review. Archives Dis Child - Fetal Neonatal Ed. 2016;101:67.

[59] Watanabe K. Recent advances in the understanding of transient abnormal myelopoiesis

in Down syndrome. Pediatr Int. 2019;61:222–229.

[60] Okamura T, Washio Y, Yoshimoto J, et al. Exchange Transfusion and Cytarabine for Transient Abnormal Myelopoiesis in Hydrops Fetalis. Acta Med Okayama. 2019;73:181–188.

[61] Gajewska-Knapik K, Impey L. Congenital lung lesions: Prenatal diagnosis and intervention. Semin Pediatr Surg. 2015;24:156–159.

[62] Witlox RS, Lopriore E, Oepkes D. Prenatal interventions for fetal lung lesions. Prenatal Diag. 2011;31:628–636.

[63] Cavoretto P, Molina F, Poggi S, et al. Prenatal diagnosis and outcome of echogenic fetal lung lesions. Ultrasound Obst Gyn. 2008;32:769–783.

[64] Peyce D. Lower accessory pulmonary artery with intralobar sequestration of lung: A Report of seven cases. J Pathology Bacteriol. 1946;58:457–467.

[65] Sepulveda W. Perinatal Imaging in Bronchopulmonary Sequestration. J Ultras Med. 2009;28:89–94.

[66] Carrilho M, Tonni G, Júnior E. Fetal cardiac tumors: prenatal diagnosis and outcomes. Rev Bras Cir Cardiov. 2015;30:VI–VII.

[67] Isaacs H. Fetal and Neonatal Cardiac Tumors. Pediatr Cardiol. 2004;25:252–273.

[68] Chao A, Chao A, Wang T, et al. Outcome of antenatally diagnosed cardiac rhabdomyoma: case series and a meta-analysis. Ultrasound Obst Gyn. 2008;31:289–295.

[69] Yuan S-M. Fetal Primary Cardiac Tumors During Perinatal Period. Pediatrics Neonatol. 2017;58:205–210.

[70] Steffensen TS, Quintero RA, Kontopoulos EV, et al. MASSIVE PERICARDIAL EFFUSION TREATED WITH IN UTERO PERICARDIOAMNIOTIC SHUNT IN A FETUS WITH INTRAPERICARDIAL TERATOMA. Fetal Pediatr Pathol. 2009;28:216–231.

[71] Grebille A, Mitanchez D, Benachi A, et al. Pericardial teratoma complicated by hydrops: successful fetal therapy by thoracoamniotic shunting. Prenatal Diag. 2003;23:735–739.

[72] Bellini C, Hennekam R, Fulcheri E, et al. Etiology of nonimmune hydrops fetalis: A systematic review. Am J Med Genet A. 2009;149A:844–851.

[73] Johnson P, Maxwell D, Tynan M, et al. Intracardiac pressures in the human fetus. Heart. 2000;84:59.

[74] Bravo-Valenzuela N, Rocha L, Nardozza L, et al. Fetal cardiac arrhythmias: Current evidence. Ann Pediatric Cardiol. 2018;11:148.

[75] Simpson JM, Milburn A, Yates RW, et al. Outcome of Intermittent Tachyarrhythmias in

the Fetus. Pediatr Cardiol. 1997;18:78–82.

[76] Simpson J. Impact of fetal echocardiography. Ann Pediatric Cardiol. 2009;2:41–50.

[77] Krapp M, Kohl T, Simpson J, et al. Review of diagnosis, treatment, and outcome of fetal atrial flutter compared with supraventricular tachycardia. Heart. 2003;89:913.

[78] Ishikawa S, Yamada T, Kuwata T, et al. Fetal Presentation of Long QT Syndrome – Evaluation of Prenatal Risk Factors: A Systematic Review. Fetal Diagn Ther. 2013;33:1–7.

[79] de Jesus G, Mendoza-Pinto C, de Jesus N, et al. Understanding and Managing Pregnancy in Patients with Lupus. Autoimmune Dis. 2015;2015:943490.

[80] Marshall DA, MacDonald KV, Heidenreich S, et al. The value of diagnostic testing for parents of children with rare genetic diseases. Genet Med. 2019;1–9.

[81] Mongiovi M, Fesslova V, Fazio G, et al. Diagnosis and Prognosis of Fetal Cardiomyopathies: A Review. Curr Pharm Design. 2010;16:2929–2934.

[82] Davey B, Szwast A, Rychik J. Diagnosis and management of heart failure in the fetus. Minerva Pediatr. 2012;64:471–492.

[83] Sivasankaran S, Sharland GK, Simpson JM. Dilated cardiomyopathy presenting during fetal life. Cardiol Young. 2005;15:409–416.

[84] Yaoita M, Niihori T, Mizuno S, et al. Spectrum of mutations and genotype–phenotype analysis in Noonan syndrome patients with RIT1 mutations. Hum Genet. 2016;135:209–222.

[85] Clarke SL, Bowron A, Gonzalez IL, et al. Barth syndrome. Orphanet J Rare Dis. 2013;8:23.

[86] Steward C, Newbury-Ecob R, Hastings R, et al. Barth syndrome: an X-linked cause of fetal cardiomyopathy and stillbirth. Prenatal Diag. 2010;30:970–976.

[87] Barth P, den Bogert VC, Bolhuis P, et al. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome): Respiratory-chain abnormalities in cultured fibroblasts. J Inherit Metab Dis. 1996;19:157–160.

[88] Makhamreh MM, Cottingham N, Ferreira CR, et al. Non-Immune Hydrops Fetalis and Congenital Disorders of Glycosylation: A Systematic Literature Review. J Inherit Metab Dis. 2019;

[89] Heling K -S., Tennstedt C, Göldner B, et al. Prenatal diagnosis of intrapulmonary arteriovenous malformation: sonographic and pathomorphological findings. Ultrasound Obst Gyn. 2002;19:514–517.

[90] Godfrey ME, Tworetzky W, Morash D, et al. Cardiac Findings in the Fetus with Cerebral Arteriovenous Malformation Are Associated with Adverse Outcome. Fetal Diagn Ther. 2017;41:108–114.

[91] Marinaş M, Mindrilă I, Zorilă G, et al. A Severe Case of Aneurysmal Malformation of the Vein of Galen, Cardiac Failure and Intrauterine Fetal Death. Curr Heal Sci J. 2018;44:76–79.

[92] Darouich S, Bellamine H, Mkaouar L, et al. Congenital Large Cutaneous Hemangioma with Arteriovenous and Arterioarterial Malformations: A Novel Association. Fetal Pediatr Pathol. 2019;38:1–6.

[93] Swamy R, Embleton N, Hale J. Sacrococcygeal teratoma over two decades: Birth prevalence, prenatal diagnosis and clinical outcomes. Prenatal Diag. 2008;28:1048–1051.

[94] Wenstrom KD, Carr SR. Fetal Surgery. Obstetrics Gynecol. 2014;124:817–835.

[95] Akinkuotu AC, Coleman A, Shue E, et al. Predictors of poor prognosis in prenatally diagnosed sacrococcygeal teratoma: A multiinstitutional review. J Pediatr Surg. 2015;50:771–774.

[96] Yanai N, Shveiky D. Fetal hydrops, associated with maternal propylthiouracil exposure, reversed by intrauterine therapy. Ultrasound Obst Gyn. 2004;23:198–201.

[97] Kazakou P, Theodora M, Kanaka-Gantenbein C, et al. Fetal hyperthyroidism associated with maternal thyroid autoantibodies: A case report. Case Reports Women's Heal. 2018;20:e00081.

[98] King J, Lachica R, Lee RH, et al. Diagnosis and Management of Hyperthyroidism in Pregnancy. Obstet Gynecol Surv. 2016;71:675–685.

[99] de Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. Am J Med Genet A. 2015;167:756–767.

[100] Bekker MN, van den Akker NM, de Mooij YM, et al. Jugular Lymphatic Maldevelopment in Turner Syndrome and Trisomy 21: Different Anomalies Leading to Nuchal Edema. Reprod Sci. 2008;15:295–304.

[101] Anuk D, Tarcan A, Alioglu B, et al. Hydrops fetalis in a neonate with down syndrome, transient myeloproliferative disorder and hepatic fibrosis. Fetal Pediatr Pathol. 2009;26:223–228.

[102] Kroes I, Janssens S, Defoort P. Ultrasound features in trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) in a consecutive series of 47 cases. Facts Views Vis Obgyn. 2014;6:245–249.

[103] Sparks TN, Thao K, Lianoglou BR, et al. Nonimmune hydrops fetalis: identifying the underlying genetic etiology. Genet Med. 2019;21:1339–1344.

[104] Jones GE, Mansour S. An approach to familial lymphoedema. Clin Med. 2017;17:552–557.

[105] Surerus E, Huggon I, Allan L. Turner's syndrome in fetal life. Ultrasound Obst Gyn. 2003;22:264–267.

[106] Brown B. The ultrasonographic features of nonimmune hydrops fetalis: a study of 30 successive patients. Can Assoc Radiologists J J L'association Can Des Radiologistes. 1986;37:164–168.

[107] Libotte F, Bizzoco D, Gabrielli I, et al. Pallister–Killian syndrome: Cytogenetics and molecular investigations of mosaic tetrasomy 12p in prenatal chorionic villus and in amniocytes. Strategy of prenatal diagnosis. Taiwan J Obstetrics Gynecol. 2016;55:863–866.

[108] Machlitt A, Tennstedt C, Körner H, et al. Prenatal diagnosis of 22q11 microdeletion in an early second-trimester fetus with conotruncal anomaly presenting with increased nuchal translucency and bilateral intracardiac echogenic foci. Ultrasound Obstetrics Gynecol. 2002;19:510–513.

[109] Public Health England. NHS Fetal Anomaly Screening Programme; Public Health England Publications. 2018

[110] Lo D, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. Lancet. 1997;350:485–487.

[111] Hu H, Wang L, Wu J, et al. Noninvasive prenatal testing for chromosome aneuploidies

and subchromosomal microdeletions/microduplications in a cohort of 8141 single pregnancies. Hum Genomics. 2019;13:14.

[112] Connell F, Gordon K, Brice G, et al. The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. Clin Genet. 2013;84:303–314.

[113] Fotiou E, Martin-Almedina S, Simpson MA, et al. Novel mutations in PIEZO1 cause an autosomal recessive generalized lymphatic dysplasia with non-immune hydrops fetalis. Nat Commun. 2015;6:8085.

[114] Coste B, Mathur J, Schmidt M, et al. Piezo1 and Piezo2 Are Essential Components of Distinct Mechanically Activated Cation Channels. Science. 2010;330:55–60.

[115] Martin-Almedina S, Martinez-Corral I, Holdhus R, et al. EPHB4 kinase–inactivating mutations cause autosomal dominant lymphatic-related hydrops fetalis. J Clin Invest. 2016;126:3080–3088.

[116] Li D, Wenger TL, Seiler C, et al. Pathogenic variant in EPHB4 results in central conducting lymphatic anomaly. Hum Mol Genet. 2018;27:3233–3245.

[117] Zhang G, Brady J, Liang W-C, et al. EphB4 forward signalling regulates lymphatic valve development. Nat Commun. 2015;6:6625.

[118] Hennekam R, Geerdink R, Hamel B, et al. Autosomal recessive intestinal lymphangiectasia and lymphedema, with facial anomalies and mental retardation. Am J Med Genet. 1989;34:593–600.

[119] Alders M, Hogan BM, Gjini E, et al. Mutations in CCBE1 cause generalized lymph vessel dysplasia in humans. Nat Genet. 2009;41:1272–1274.

[120] Hogan BM, Bos FL, Bussmann J, et al. ccbe1 is required for embryonic lymphangiogenesis and venous sprouting. Nat Genet. 2009;41:396–398.

[121] Melber DJ, Andreasen TS, Mao R, et al. Novel mutation in CCBE 1 as a cause of recurrent hydrops fetalis from Hennekam lymphangiectasia-lymphedema syndrome-1. Clin Case Reports. 2018;6:2358–2363.

[122] Connell F, Kalidas K, Ostergaard P, et al. Linkage and sequence analysis indicate that CCBE1 is mutated in recessively inherited generalised lymphatic dysplasia. Hum Genet. 2010;127:231–241.

[123] Alders M, Al-Gazali L, Cordeiro I, et al. Hennekam syndrome can be caused by FAT4 mutations and be allelic to Van Maldergem syndrome. Hum Genet. 2014;133:1161–1167.

[124] Brouillard P, Dupont L, Helaers R, et al. Loss of ADAMTS3 activity causes Hennekam lymphangiectasia–lymphedema syndrome 3. Hum Mol Genet. 2017;26:4095–4104.

[125] Boone PM, Paterson S, Mohajeri K, et al. Biallelic mutation of FBXL7 suggests a novel form of Hennekam syndrome. Am J Med Genet A. 2019; 182(1):189-194.

[126] Brice G, Child A, Evans A, et al. Milroy disease and the VEGFR-3 mutation phenotype. J Med Genet. 2005;42:98.

[127] Boudon E, Levy Y, Abossolo T, et al. Antenatal presentation of hereditary lymphedema type I. Eur J Med Genet. 2015;58:329–331.

[128] Daniel-Spiegel E, Ghalamkarpour A, Spiegel R, et al. Hydrops fetalis: an unusual prenatal presentation of hereditary congenital lymphedema. Prenatal Diag. 2005;25:1015–1018.

[129] Ghalamkarpour A, Morlot S, Raas-Rothschild A, et al. Hereditary lymphedema type I associated with VEGFR3 mutation: the first de novo case and atypical presentations. Clin Genet. 2006;70:330–335.

[130] Brice G, Mansour S, Bell R, et al. Analysis of the phenotypic abnormalities in lymphoedema-distichiasis syndrome in 74 patients with FOXC2 mutations or linkage to 16q24. J Med Genet. 2002;39:478.

[131] Sargent C, Bauer J, Khalil M, et al. A five generation family with a novel mutation in FOXC2 and lymphedema worsening to hydrops in the youngest generation. Am J Med Genet A. 2014;164:2802–2807.

[132] Ghalamkarpour A, Debauche C, Haan E, et al. Sporadic In Utero Generalized Edema Caused by Mutations in the Lymphangiogenic Genes VEGFR3 and FOXC2. J Pediatrics. 2009;155:90–93.

[133] Aoki Y, Niihori T, Inoue S, et al. Recent advances in RASopathies. J Hum Genet. 2015;61:33–39.

[134] Joyce S, Gordon K, Brice G, et al. The lymphatic phenotype in Noonan and Cardiofaciocutaneous syndrome. Eur J Hum Genet. 2015;24:690–696.

[135] Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 Mutations in Noonan Syndrome: Molecular Spectrum, Genotype-Phenotype Correlation, and Phenotypic Heterogeneity. Am J Hum Genetics. 2002;70:1555–1563.

[136] Bouchikhi I, Belhassan K, Moufid F, et al. Noonan syndrome-causing genes: Molecular update and an assessment of the mutation rate. Int J Pediatrics Adolesc Medicine. 2016;3:133–142.

[137] Staboulidou I, Pereira S, de Cruz J, et al. Prevalence and Outcome of Absence of Ductus Venosus at 11+0 to 13+6 Weeks. Fetal Diagn Ther. 2011;30:35–40.

[138] Vigneswaran TV, Homfray T, Allan LD, et al. Persistently elevated nuchal translucency and the fetal heart. J Maternal-fetal Neonatal Medicine. 2017;31:1–13.

[139] de Mooij YM, van den Akker NM, Bekker MN, et al. Aberrant lymphatic development in euploid fetuses with increased nuchal translucency including Noonan syndrome. Prenatal Diag. 2011;31:159–166.

[140] Sudrié-Arnaud B, Marguet F, Patrier S, et al. Metabolic causes of nonimmune hydrops fetalis: A next-generation sequencing panel as a first-line investigation. Clin Chim Acta. 2018;481:1–8.

[141] Gimovsky AC, Luzi P, Berghella V. Lysosomal storage disease as an etiology of nonimmune hydrops. Am J Obstet Gynecol. 2015;212:281–290.

[142] Vianey-Saban C, Acquaviva C, Cheillan D, et al. Antenatal manifestations of inborn errors of metabolism: biological diagnosis. J Inherit Metab Dis. 2016;39:611–624.

[143] Sheth J, Mistri M, Shah K, et al. JIMD Reports, Volume 35. 2016;47–52.

[144] Braverman NE, Raymond GV, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016;117:313–321.

[145] Dursun A, Gucer S, Ebberink M, et al. Zellweger syndrome with unusual findings: non-immune hydrops fetalis, dermal erythropoiesis and hypoplastic toe nails. J Inherit Metab Dis. 2009;32:345–348.

[146] Bianconi SE, Cross JL, Wassif CA, et al. Pathogenesis, epidemiology, diagnosis and clinical aspects of Smith–Lemli–Opitz syndrome. Expert Opin Orphan D. 2015;3:267–280.

[147] Maymon R, Ogle R, Chitty L. Smith–Lemli–Opitz syndrome presenting with persisting nuchal oedema and non-immune hydrops. Prenatal Diag. 1999;19:105–107.

[148] Putnam AR, Szakacs JG, Opitz JM, et al. Prenatal death in Smith–Lemli–Opitz/RSH syndrome. Am J Med Genet A. 2005;138A:61–65.

[149] Smith DW, Lemli L, Opitz JM. A newly recognized syndrome of multiple congenital anomalies. J Pediatrics. 1964;64:210–217.

[150] Warman ML, Cormier-Daire V, Hall C, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;155:943–968.

[151] Milks KS, Hill LM, Hosseinzadeh K. Evaluating skeletal dysplasias on prenatal ultrasound: an emphasis on predicting lethality. Pediatr Radiol. 2017;47:134–145.

[152] Barros C, de Rezende G, Júnior E, et al. Prediction of lethal pulmonary hypoplasia by means fetal lung volume in skeletal dysplasias: a three-dimensional ultrasound assessment. J Maternal-fetal Neonatal Medicine. 2015;29:1–6.

[153] Krakow D, Lachman RS, Rimoin DL. Guidelines for the prenatal diagnosis of fetal

skeletal dysplasias. Genet Med. 2009;11:127.

[154] Parilla BV, Leeth EA, Kambich MP, et al. Antenatal Detection of Skeletal Dysplasias. J Ultras Med. 2003;22:255–258.

[155] Geister KA, Camper SA. Advances in Skeletal Dysplasia Genetics. Annu Rev Genom Hum G. 2015;16:1–29.

[156] Krakow D. Skeletal Dysplasias. Clin Perinatol. 2015;42:301–319.

[157] Chitty LS, Mason S, Barrett AN, et al. Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach. Prenatal Diag. 2015;35:656–662.

[158] Bellini C, Donarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: An update. Am J Med Genet A. 2015;167:1082–1088.

[159] Agakidis C, Agakidou E, Sarafidis K, et al. Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked Syndrome Associated With a Novel Mutation of FOXP3 Gene. Frontiers Pediatrics. 2019;7:20.

[160] Shanes E, Propst L, Ouyang DW, et al. Recurrent Non-immune Fetal Hydrops Associated With IPEX Syndrome. Pediatric Dev Pathology Official J Soc Pediatric Pathology Paediatr Pathology Soc. 2019;1093526619834809.

[161] Xavier-da-Silva M, Moreira-Filho CA, Suzuki E, et al. Fetal-onset IPEX: Report of two families and review of literature. Clin Immunol. 2015;156:131–140.

[162] Schrander-Stumpel C, Spruyt L, Curfs L, et al. Kabuki syndrome: Clinical data in 20 patients, literature review, and further guidelines for preventive management. Am J Med Genet A. 2005;132A:234–243.

[163] Long A, Sinkovskaya ES, Edmondson AC, et al. Kabuki syndrome as a cause of non-immune fetal hydrops/ascites. Am J Med Genet A. 2016;170:3333–3337.

[164] Quinlan-Jones E, Lord J, Williams D, et al. Molecular autopsy by trio exome sequencing (ES) and postmortem examination in fetuses and neonates with prenatally identified structural anomalies. Genet Med. 2019;21:1065–1073.

[165] Kamata S, Nose K, Ishikawa S, et al. Meconium peritonitis in utero. Pediatr Surg Int. 2000;16:377–379.

[166] Mandakini P, Ashwin D, Manisha R, et al. Urorectal septum malformation presenting as nonimmune hydrops fetalis. Prenatal Diag. 2006;26:582–584.

[167] Kim C, Kim S, Yang Y, et al. A case of recurrent infantile polycystic kidney associated with hydrops fetalis. Yonsei Med J. 1988;30:95–103.

[168] Rodríguez MM, Chaves F, Romaguera RL, et al. Value of Autopsy in Nonimmune Hydrops Fetalis: Series of 51 Stillborn Fetuses. Pediatr Devel Pathol. 2002;5:365–374.

[169] Çetinkaya M, Durmaz O, Büyükkale G, et al. Neonatal Bartter syndrome and unilateral ectopic renal cyst as new renal causes of hydrops fetalis: two case reports and review of the literature. J Maternal-fetal Neonatal Medicine. 2013;26:1147–1150.

[170] Debray F-G, de Halleux V, Guidi O, et al. Neonatal Liver Cirrhosis Without Iron Overload Caused by Gestational Alloimmune Liver Disease. Pediatrics. 2012;129:e1076–e1079.

[171] da Rocha C, Guedes R, Kieling C, et al. Neonatal Liver Failure and Congenital Cirrhosis due to Gestational Alloimmune Liver Disease: A Case Report and Literature Review. Case Reports Pediatrics. 2017;2017:1–7.

[172] Whitington PF, Kelly S, Taylor SA, et al. Antenatal Treatment with Intravenous Immunoglobulin to Prevent Gestational Alloimmune Liver Disease: Comparative Effectiveness of 14-Week versus 18-Week Initiation. Fetal Diagn Ther. 2018;43:218–225.

[173] Kaiser I. Ballantyne and triple edema. Am J Obstet Gynecol. 1971;110:115–120.

[174] Gedikbasi A, Oztarhan K, Gunenc Z, et al. Preeclampsia due to fetal non-immune hydrops: mirror syndrome and review of literature. Hypertens Pregnancy. 2010;30:322–330.

[175] Navarro-Perez SF, Corona-Fernandez K, Rodriguez-Chavez JL, et al. Significant Clinical Manifestations in Ballantyne Syndrome, after a Case Report and Literature Review: Recognizing Preeclampsia as a Differential Diagnosis. Case Reports Obstetrics Gynecol. 2019;2019:1–7.

[176] Braun T, Brauer M, Fuchs I, et al. Mirror syndrome: a systematic review of fetal associated conditions, maternal presentation and perinatal outcome. Fetal Diagn Ther. 2010;27:191–203.

[177] Allarakia S, Khayat HA, Karami MM, et al. Characteristics and management of mirror syndrome: a systematic review (1956–2016). J Perinat Med. 2017;45:1013–1021.

[178] Gherman R, Incerpi M, Wing D, et al. Ballantyne syndrome: is placental ischemia the etiology? J Maternal-fetal Medicine. 1998;7:227–229.

Table 1. Structural cardiac malformations causing fetal hydrops.

Structural heart disease	**Pathophysiology of fetal hydrops**
Ebstein's anomaly	Tricuspid valve regurgitation, impact on left ventricle
Common arterial trunk with truncal valve stenosis	Obstruction to left and right ventricles
Hypoplastic left heart	If severe atrioventricular valve regurgitation, severely restrictive atrial septum
Left atrial isomerism	Atrioventricular block or severe atrioventricular valve regurgitation
Discordant AV connections	Atrioventricular block, severe tricuspid regurgitation

Figure 1. 13 weeks gestation fetus showing significantly increased nuchal translucency (indicated with broken yellow line) in a fetus with Noonan syndrome.

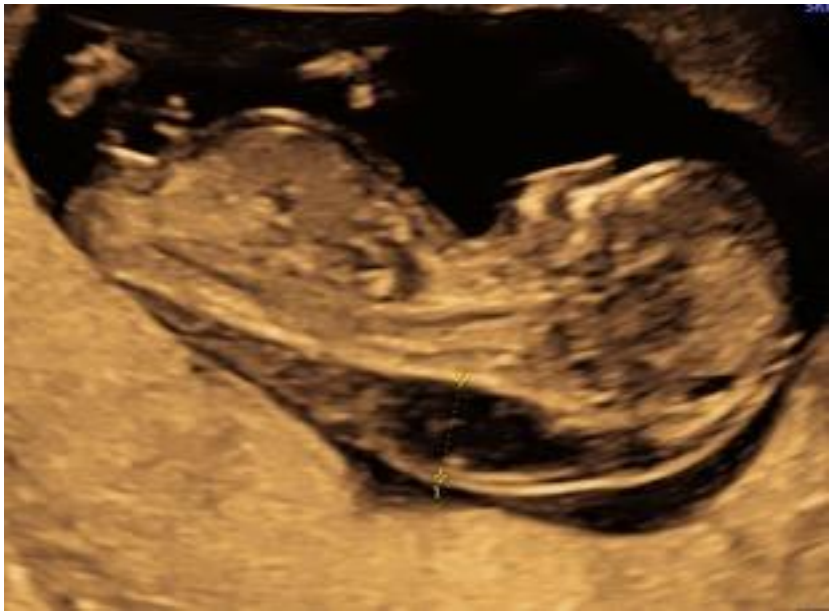


Figure 2. 19 weeks gestation fetus demonstrating fetal hydrops with fluid seen accumulating in the abdominal cavity (ascites, blue arrow) as well as a small pericardial effusion (red arrow) and subcutaneous skin oedema (green arrow) in a fetus with a mutation in *PIEZO1*(generalised lymphatic dysplasia).

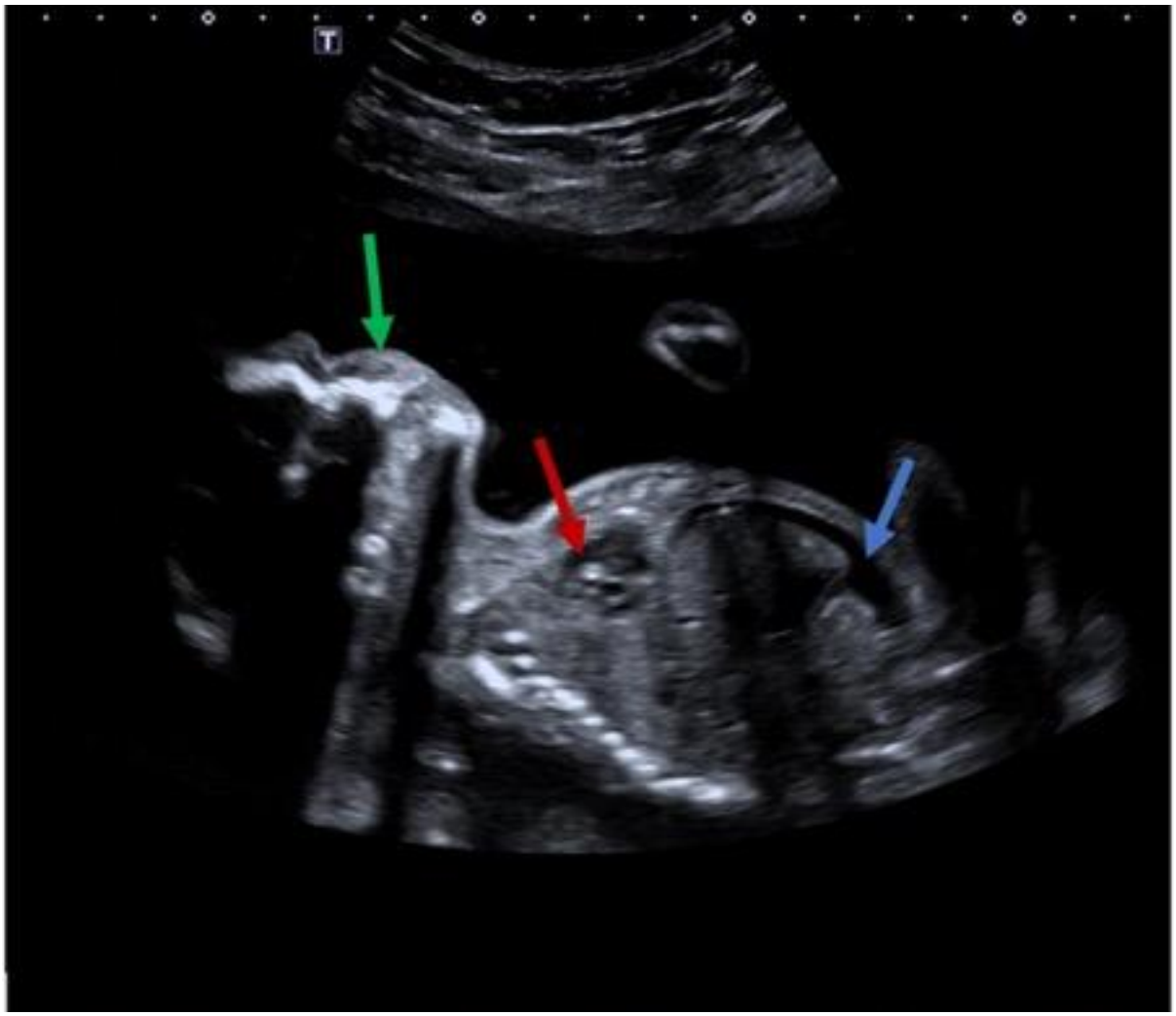
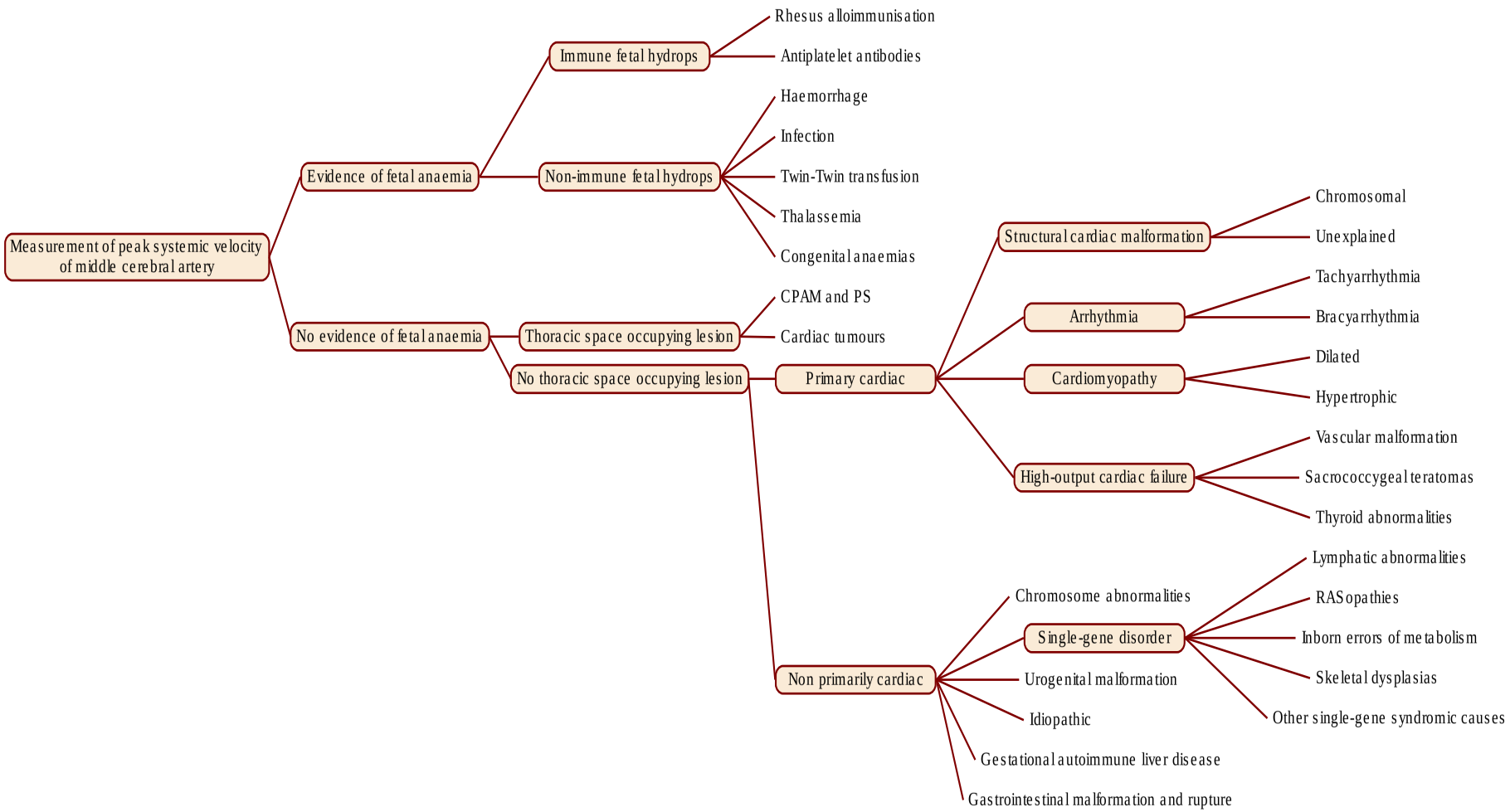


Figure 3. Illustration of the process by which a clinician may prioritise investigations to identify the underlying cause of fetal hydrops presenting after the first trimester.

https://www.plantuml.com/plantuml/svg/hPTVRzis4C3V_IaEVbQ6ENOpe846PDcm16Yo8cx...



Hydrops decision tree