Fetal Hydrops

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13.1 Introduction

Fetal hydrops (or hydrops fetalis) is not a disease but a clinicopathological term, describing the final stage of abnormal fetal fluid homeostasis. Increased fluid loss into the fetal tissues and through the serosal surface into the serous body cavities could be due to increased hydrostatic pressure in the capillaries, decreased plasma oncotic pressure (i.e. hypoproteinaemia), leaking capillary walls and abnormal development of the lymphatic system. The most common cause of increased pressure in the venous system is cardiac failure. There are other unique fetal physiological factors, such as characteristics of fetal microcirculation and immaturity of the developing organs, which make fetuses more vulnerable for progressive edema formation.

Advances in ultrasonography, genetic and molecular testing have improved prenatal diagnosis. Even if fetal therapies are available for many types of non-immune fetal hydrops (NIFH), mortality rate is still high and this is strongly linked to the underlying etiologies.

NIHF includes cases not caused by red cell alloimmunisation and is categorised based on the underlying fetal and placental etiologies. There is a growing number of diseases being described in association with NIFH and categorisation of these entities is challenging. Many genetic diseases and syndromes with multiple organ abnormalities are difficult to classify into one organ system disease. For example, Down syndrome is associated with cardiac malformation, lymphatic dysplasia and transient abnormal myelopoiesis. The most frequent categories of NIFH are chromosomal, cardiovascular, infectious, hematologic, lymphatic, genetic and idiopathic diseases [1].

Many diseases have characteristic features or structural anomalies suggesting the diagnosis on antenatal scans. Other cases, for example in lysosomal storage disease or lymphatic dysplasia, cannot be diagnosed on scan and further investigations should be included in the diagnostic work up. Evolving new molecular techniques (eg. analysis of targeted panels of genes with next generation sequencing, whole genome or exome sequencing) has become more available and integrated into clinical practice.

Precise diagnosis of NIHF is important in order to counsel families about prognosis and recurrence risk, guide treatment decisions and anticipate neonatal care requirements. Therefore, all patients with fetal hydrops should be referred to tertiary care centres for evaluation and treatment.

13.2 Global Patterns and Incidence

Traditionally, fetal hydrops has been divided broadly into immune and non-immune subcategories. The prototype of the immunologic group is fetal hemolytic anemia due to Rhesus alloimmunization. Until the late twentieth century, it was the foremost cause of hydrops in the Western world. With the introduction of anti-D prophylaxis for Rhesus disease, early routine screening, diagnostic and therapeutic interventions in fetal medicine have seen a significant reduction in the incidence of the immune hydrops.

Fetal hydrops can be detected throughout the pregnancy. In the first half of the pregnancy, chromosomal abnormality is the most frequently implicated cause [2]. From the second half of the pregnancy, there is a marked geographic variation in patterns of causation. Cardiovascular disease is most frequent in the West and alpha thalassemia is still a major problem in some parts of Asia [3–6]. A significant portion of the cases are still due to an unknown cause (i.e. idiopathic category) in most of the published studies.

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Therapeutic and diagnostic improvements have also changed the incidence of hydrops and the survival rate. Uptake of early termination of pregnancy may have also altered the pattern and the frequency of hydrops observed in later pregnancy [7].

Nowadays, non-immunological disorders cause more than 85% of hydrops fetalis with an incidence of around 1 in 2000–3000 pregnancies [2]. In a study from the UK, 87 hydrops cases (immune and non-immune) were detected amongst 13,980 pregnancies giving the rate of 6.2 to 1000 pregnancies [2], 4 of which were related to red cell isoimmunization (4.6%) and 83 cases (95.4%) were non-immune related hydrops. Trainor et al. reported that the incidence of live born immune and non-immune hydrops was 1.34 to 1000, and 80% of these cases were non-immune hydrops [8]. Takci et al. reported a slightly higher rate of 3.8 per 1000 live births with an incidence of non-immune hydrops in 2 per 1000 live births [9].

13.3 Morbidity and Mortality

The mortality rate in fetal hydrops is generally considered to be high [4, 10–13] (Table 13.1). Cases diagnosed in early pregnancy appear to have a higher rate of aneuploidy and mortality rate [17]. He et al. found that 52.3% of chromosomal abnormalities in NIFH were diagnosed between 15 and 19 weeks [16]. Ota et al. [15] had similar findings that before 22 weeks the most frequent etiology was chromosomal abnormality, whereas after 22 weeks, cardiac structural anomalies were found most frequently. In cases of aneuploidy, pregnancy is more likely to progress to miscarriage or be terminated before 22 weeks. Early detection of fetal hydrops is followed by termination of the pregnancy between 7.1% and 95.2% in the published studies [14, 16]. In a study from Southern China, termination of pregnancy was very high (95.2%) and the two most common causes of NIHF was Hb Bart's syndrome (61.8%) and chromosomal abnormalities (13.5%) [16]. High prevalence of Hb Bart's disease and other alpha - thalassemia in Southeast Asian countries has been well recognised [16, 18].

Cases of spontaneous intrauterine death range between 3% and 55.5% [11, 16], and according to Fukushima et al. fetal losses before and after 22 weeks are very similar, 28.4% and 27.1% respectively [11].

Approximately 50% of the antenatally diagnosed hydrops cases are born alive, but there is wide variation between pregnancy outcomes (1.8% to 83.2%). This is likely due to differences in geographic distribution of certain etiologies in the analysed populations. A high number of Hb Bart's syndrome cases was reported in the study from South China [16]. Neonatal death ranges between 22.7% and 66.7% [12, 16] and neonatal outcome has been associated with fetal maturity, condition at birth (Apgar scores) and respiratory support requirements [9, 19]. The underlying cause of fetal hydrops is another important contributory factor to neonatal mortality with the highest mortality rates being seen amongst neonates with congenital anomalies (57.7%) and the lowest amongst neonates with congenital chylothorax (5.9%) [19]. Better survival rates were reported with later detection of fetal hydrops by Fukushima et al. In this study, live born fetuses with NIFH constituted 18.8%, 33.3%, 44.6%, and 66.7% of the cases, corresponding to the time of diagnoses before 22 weeks, between 23 and 25 weeks, between 26 and 29 weeks and over 30 weeks gestation [11]. The same study followed up 56 ex-hydropic infants and they found that even if the survival rate increased with later detection of hydrops, intact neurological development had an inverse correlation with the gestational age. 51.7% of surviving babies were normally developed at 1 year follow up; 71.5%, 60.0%,

Table 13.1 Mortality of nonimmune fetal hydrops

	Termination of pregnancy (lethal and nonlethal causes)	Intrauterine death	Live birth	Neonatal death of live born cases
Heinonen et al. (2000) [10]	72.5% (42/58)	15.5% (9/58)	12% (7/58)	28.57% (2/7)[a]
Sohan et al. (2001) [2][b]	37.3% (31/83)	19.2% (16/83)	43.3% (36/83)	30.55% (11/36)
Fukushima et al. (2011) [11][c]	10.8% (26/240)	<22 week 28.4% (35/240) >22 week 27.1% (34/240)	60.4% (145/240)	37.2% (54/145)
Santo et al. (2011) [12]	21.2% (15/71)	17% (12/71)	62% (44/71)	22.7% (10/44)
Moreno et al. (2013) [7]	7.5% (4/53)	30% (16/53)	43.4% (23/53)	43.5% (10/23)
Ng et al. (2013) [13]	31% (9/29)	3.4% (1/29)	65.5% (19/29)	57.9% (11/19)
Yeom et al. (2015) [14]	7.1% (3/42)	9.5% (4/42)	83.3% (35/42)	54.2% (19/35)
Ota et al. (2016) [15][d]	14.8% (16/108)	38% (41/108)	47.2% (51/108), 55.4% (51/92)	27.4% (14/51)
He et al. (2017) [16]	95.2% (459/482)	3% (14/482)	1.8% (9/482)	66.7% (6/9)
Gilby et al. (2018) [17]	29% (37/131)	31% (29/131)	69% (65/131)	44.6% (29/65)

[a]2 perinatal deaths counted amongst neonatal deaths
[b]Study of 87 hydrops cases: 4 cases were rhesus alloimmunisation which survived until neonatal period and not included in this table
[c]Study analyzed 240 non-immune hydrops cases, of which 214 were not terminated
[d]Study included 108 cases of non-immune fetal hydrops cases, of those 16 were terminated

50.0%, and 43.3% of which was detected before 22 weeks, between 22 and 25 weeks, between 26 and 29 weeks, and over 30 weeks of gestation. In the same study, 32.8% of the followed infants had some evidence of neurological impairment and 15.5% had suspected neurological abnormalities. 57.9% of the cases was found to have chromosomal abnormalities, low birth weight and traumatic brain injury, in addition to features of hydrops fetalis, contributing to neurological outcome [11].

Haverkamp et al. followed 28 NIFH survivors for neurological, cognitive and motor functions. They found that the survival was related to the severity of intrauterine hydrops (i.e., the less severe, the better the survival) and confirmed that the neurological prognosis was more related to the underlying disease. In this study, 85.7% (24/28) of the patients had normal neurological status, 7.2% had minor dysfunctions and 7.2% had spastic cerebral paresis [20].

Ota et al. studied 92 cases with NIHF. 51 babies were live born (55.4%, 51/92), and of those, 33 babies survived beyond 1 year (65%, 33/51), 18 babies had developmental delay or/and other abnormalities related to underlying etiology of hydrops, for example cardiac structural defects (35.3% 18/51), and 15 babies were intact (29.4%, 15/51) [15].

13.4 Clinical Presentation

Fetal hydrops may present at any gestation from the first trimester to term. It may be unexpectedly recognised at birth on occasion and some cases have been reported to be resolved antenatally. Owing to improvements in diagnostic techniques, detection more often occurs at early gestations and more precise diagnosis supports better correlation with risk and outcome, improves parental counseling and guides treatment decisions (*Investigation of fetal hydrops*, as below).

In the first trimester, hydrops is usually detected at an asymptomatic stage during routine ultrasound scanning or in spontaneous miscarriages. These are usually syndromic cases with identifiable chromosomal abnormalities. Prominent translucencies, so called fetal "space-suit" hydrops, indicate an even higher risk of chromosomal abnormality than isolated nuchal translucency [21]. In early gestational age, these pregnancies usually result in spontaneous miscarriage, intrauterine fetal death or elective termination [2, 22]. In the second half of pregnancy, especially in the 3rd trimester, hydrops is more often due to other etiologies, such as cardiac malformations.

Typical presentation is with generalized, subcutaneous or nuchal edema and serous effusions in pleural, pericardial and peritoneal cavities. Owing to excessive fluid accumulation in soft tissue compartments, organs and body cavities, the body measurements are large for gestational age. Fetal tachycardia, decreased fetal movements, abnormal serum screening and antepartum hemorrhage are also featured in some of the cases.

The placenta is typically enlarged, thickened and edematous. Polyhydramnios and maternal edema (mirror syndrome) may be present. Following the initial ultrasound recognition of fetal hydrops, ideally, mothers should be referred to a tertiary fetal and maternal medicine center for further investigation and management [23].

13.5 Fetal Fluid Dynamics

The fetus has very high total body water content. In the embryo, 90–95% of the body weight is of fluid, which gradually decreases to about 80% by 8 months gestation and to around 75% at term [22].

As in adults, edema is caused by accelerated water flow through the capillary walls into the extravascular spaces and/or impaired reabsorption of fluid from interstitial tissue back to the circulation. Trans-capillary filtration is controlled by hydrostatic and colloid osmotic pressures (Starling forces) as in adults. There are, however, unique physiological fetal factors promoting abnormal tissue fluid accumulation.

The fetal capillary filtration coefficient is increased compared to adults. This means that the capillary wall is more permeable with greater water flow and protein movement with less capacity to retain fluid in the intravascular compartments [24]. Immature liver produces low amounts of albumin [1], resulting in low protein levels. The fetal interstitial space is more compliant and the interstitium can accommodate more fluid without significant increase in the hydrostatic pressure [24, 25]. Therefore, the fetal lymph flow is four- to fivefold higher in lymphatic vessels than in adults to enable return of excess fluid and protein from the interstitium into the circulation [26]. The lymph flow is maintained until the central venous pressure is negative or low. When the venous pressure rises to 15 mmHg, lymphatic drainage of the interstitium is reduced and/or stops (compared with 25–30 mmHg in the adults). Consequently, a slight increase in the central venous pressure rapidly leads to interstitial fluid accumulation [27].

Based on their experiment on volume control in sheep, Faber et al. stated, "the flow of water from mother to fetus is modulated to control fetal circulation, regardless of the volume of water already present in the conceptus". They also concluded that no fetal organ controls the fetal fluid volume and the main determinants in fluid balance are cardiac, circulatory, renal and placental properties [28]. Placenta has an important role in fetal fluid balance [29].

Fetal fluid homeostasis and maintaining perfusion of critical organs such as brain, adrenals and heart (i.e. blood redistribution), are under hormonal, renal and behavioural (i.e., swallowing) control [30]. The gestational age and, therefore,

the development status of these reflexes as well as the hormones have significant impact on fluid homeostasis. Angiotensin II has a central role in blood pressure regulation and diuresis. Natriuretic peptides (ANP, BNP), which respond to volume load and hyperosmolality and are effective vasoconstrictors [31]. Aldosterone has a limited role *in utero* due to immaturity of this regulatory mechanism. AVP (arginine vasopressin) decreases water reabsorption in the collecting duct and reduces urine concentration. However, this has a lesser effect in the immature kidney [30].

13.5.1 Amniotic Fluid

The amniotic fluid surrounds the fetus, provides mechanical protection and space for normal growth and development. It contains, amongst others, nutrients, growth factors and antimicrobial peptides. Its volume, production and chemical composition alters throughout a pregnancy.

In early gestation, the liquor is filtered from maternal plasma across the fetal membranes, based on hydrostatic and osmotic forces. Around 10 weeks gestation, the fetus begins to produce urine which is secreted into the amniotic sac. In late gestation, urine becomes the largest source of amniotic fluid [32].

In the early fetal period, the relationship of the amniotic fluid volume and fetal size is linear. Amniotic fluid volume increases from about 25 ml at 10 weeks to around 400 ml at 20 weeks [33]. The diffusion is bidirectional and crosses the non-keratinized skin and amniotic epithelium lined surface (i.e. umbilical cord and chorionic plate) [34]. At this stage, the amniotic fluid and the fetal extracellular fluid composition is very similar. Hence, the amniotic fluid is regarded as an extracorporeal extension of the fetal extracellular fluid compartment.

Following keratinization of the skin (beginning at 19–20 weeks and complete by 25 weeks), amniotic fluid production is more controlled and the relationship between the fetal size and the amniotic fluid volume is no longer linear. There are various pathways of materno-fetal fluid exchange. The two main sources of amniotic fluid are fetal urine and lung fluid secretions.

Urine becomes the largest source of amniotic fluid, and excess lung fluid flows out of the trachea and contributes up to one third of amniotic fluid volume [35, 36]. It is worth mentioning that amniotic fluids are also swallowed and, in congenital malformation resulting in disruption in fetal swallowing, is associated with excess amniotic fluid volume.

The intramembranous pathway (across the amniotic membranes into fetal circulation) and transmembrane pathway (across the fetal membranes into the uterine circulation) has also been described [37–39]. Trans-cellular vesicular transport of the amniotic fluid into the intramembranous microvasculature has been suggested [37]. This is, though, partly regulated by aquaporin water channels [29, 40, 41]. Vascular endothelial growth factor (VEGF) in addition to regulating growth of the blood vessels in the fetal surface of the placenta and in the membranes, it also increases vascular permeability enhancing intramembranous amniotic fluid absorption [42].

By 28 weeks, the amniotic fluid volume is around 800 ml and stays at about this volume until term. After 42 weeks, it declines to around 400 ml [27].

13.6 Causes and Mechanisms of Fetal Hydrops

The list of diseases, which have been associated with hydrops fetalis, is long and ever-expanding with new entities (Table 13.2). Two main categories are immune and non-immune hydrops fetalis, the latter further classified based on the underlying etiologies. In many cases, the underlying pathophysiological processes are complex. One disease process can alter normal physiology in many ways and other etiologies can share the same pathophysiological mechanism. The most common diseases and the underlying mechanisms leading to fluid accumulation in the fetal tissues and body cavities are summarised in Table 13.3. Interaction between the main pathophysiological processes and fetal characteristics in the *in utero* setting are demonstrated in Fig. 13.1.

Bellini et al. systematically reviewed the literature between 1979 and 2007 [1] and 2008 and 2013 [216], and collected data from carefully selected publications describing 5437 and 1338 cases with nonimmune fetal hydrops respectively. They used the same diagnostic categories and noted some changes in the percentages of each category but due to the small number of cases in the second study they interpreted the findings cautiously. One of their findings was an increase in cases with lymphatic dysplasia which was likely to reflect increasing awareness of lymphatic abnormalities in fetal hydrops, especially in idiopathic cases. Despite this finding, however, cases in the idiopathic category increased. In both studies [1, 216] the most frequent categories of NIFH were cardiovascular (21.7% and 20.1%), idiopathic (17.8% and 19.8%), hematologic (10.4% and 9.3%), chromosomal (13.4% and 9.0%), lymphatic (5.7% and 15.0%) syndromic (4.4% and 5.5%) and infectious disease (6.7% and 7.0%). Table 13.4 also includes further studies published since 2015.

Table 13.2 Diseases associated with hydrops fetalis

Cardiac abnormalities	*Arrhythmias*
Structural abnormalities	Aorto-left ventricular tunnel [60]
Complex anomaly with ambiguous cardiac situs [43, 44]	Supraventricular tachycardia [61, 62]
Tetralogy of Fallot [43]	Paroxysmal atrial tachycardia [61]
Hypoplastic left heart syndrome [45, 46]	Junctional ectopic tachycardia [63]
Transposition of great arteries [44, 47]	Complete heart block [64–66]
Truncus arteriosus [45, 47]	Complete heart block and maternal connective tissue disease [67, 68]
Atrioventricular canal defect [43, 48]	Bradycardia [45]
Double outlet right ventricle [49, 50]	Arrhythmia and conduction system anomaly [62, 68]
Single ventricle [47]	Tachyarrhythmia—virus induced [69]
Pulmonary valve atresia [48, 51]	Wolff–Parkinson–White syndrome [70]
Absent pulmonary valve + EFE [43, 52]	Long QT syndrome [71]
Aortic valve stenosis/atresia [48, 53]	*Other cardiac pathology*
Tricuspid valve atresia [44, 47]	Myocarditis [71]
Tricuspid valve atresia and ectopia cordis [48]	Myocardial infarction (coronary artery embolus) [43]
Ebstein's anomaly [49]	Cardiomyopathy [47, 48]
Mitral atresia + EFE [54]	Noncompaction cardiomyopathy [72]
Atrial septal defect [47]	Premature closure of foramen ovale [73–75]
Large ventricular septal defect [47, 55]	Premature closure of ductus arteriosus [76–79]
Noonan syndrome [56]	Endocardial fibroelastosis ± hepatitis [44, 79]
Arcadia (twin pregnancy) [43, 57]	Right Atrial Aneurysm [80]
Aorto-Left Ventricular Tunnel [58]	Cardiac Diverticulum [81]
Coronary artery fistula [59]	
Vascular abnormalities	**Chromosomal/genetic anomalies**
Hemangioma [44, 82, 83]	45XO [43, 102]
Atrial angioma [84]	90XX [103]
Coronary artery embolus [43]	Trisomy 21 [47, 53]
Generalised arterial calcification (of infancy) [85]	Trisomy 18 [44]
Descending thoracic aortic aneurysm [85]	Trisomy 13 [96, 104]
Abdominal aortic coarctation [86]	Trisomy 15 [105]
Meningeal angiomatosis [57]	Triploidy [47]
Megalencephaly—capillary malformation syndrome [87]	Trisomy 10 mosaicism [106]
Vena caval thrombus [88]	Pallister-Killian syndrome (tetrasomy 12p) [107]
Superior caval vein obstruction [89]	Partial trisomy 19q [108]
Agenesis of ductus venosus [90–92]	Mosaic tetrasomy 9p [109]
Agenesis of portal or hepatic veins [93]	Unbalanced translocation t(3;7) [110]
Abnormal course of inferior vena cava [93]	Unbalanced translocation t(8;11) [111]
Diffuse lymphangiectasia [94, 95]	1p36 deletion [112]
Cystic hygroma [44, 55]	6p deletion [113]
Familial pulmonary lymphatic hypoplasia [96]	Interstitial deletion 10q22.3-q24.1 [114]
Hennekam lymphangiectasia—lymphedema syndrome1[97, 98]	22p11 microdeletion [115]
Hereditary lymphedema syndrome, *FOXC2* mutation [99]	Distal 5q duplication [116]
Capillary malformation—AV malformation (*RASA1* mutation) [100]	c.4A>G *SHOC2* mutation [117]
Generalized lymphatic dysplasia, *PIEZO1* variant [99, 101]	IPEX syndrome (*FOXP3* mutation) [118]
Metabolic diseases	**Anemia and other hematological diseases**
Infantile Gaucher [45, 71]	Rhesus incompatibility [134]
Beta glucuronidase deficiency [119]	ABO incompatibility [65, 135]
Mucopolysaccharidosis [120]	Kell incompatibility [136, 137]
Sialidosis [121]	Alpha-thalassaemia [47]
Neuraminidase deficiency [122]	Hemoglobin Bart's [138–140]
Galactosialidosis [123]	Hemophilia A [96]
Niemann-Pick [124]	Pyruvate kinase deficiency [141, 142]
GM_1, gangliosidosis [55]	Glucose-6-phosphate dehydrogenase deficiency [143, 144]
Long-chain acyl-coenzyme A dehydrogenase def. [125]	Diamond–Blackfan syndrome [145, 146]
Fatal perinatal neuromuscular glycogenosis (type IVA) [125]	Dyserythropoietic anemia [147, 148]
Glycogenosis type IV [126]	Congenital xerocytosis [149]
Carnitine deficiency [127]	Transient myeloproliferative disorder in Trisomy 21 [150]
Neonatal haemochromatosis [128]	Familial hemophagocytic lymphohistiocytosis [151–153]
Congenital erythropoietic porphyria (Gunther disease) [129]	Chronic fetomaternal hemorrhage [72, 154]
Congenital disorder of glycosylation [130, 131]	Fetomaternal hemorrhage (choriocarcinoma) [155, 156]
Multiple sulfatase deficiency [132]	Hemorrhage into fetal organs
Autophagic vacuolar myopathy-like disorder [133]	Intracranial [157, 158]
	Intra-abdominal [159]

(continued)

Table 13.2 (continued)

Congenital infections
Parvovirus B19 [160–162]
CMV [47]
Human Herpes virus Type 1 [45]
Rubella virus [95]
Toxoplasmosis [163]
Syphilis [164]
Coxsackie virus [165]
Adenovirus [69, 166]
Candida [167]
Enterovirus [168]
Zika virus [169, 170]

Gastrointestinal and liver abnormalities
Oesophageal atresia [176]
Jejunal atresia [176]
Small intestinal volvulus [158]
Intestinal infarction [47]
Intestinal obstruction [104]
Hepatitis [44]
Hepatic necrosis [44]
Cirrhosis [44]

Musculoskeletal abnormalities
Achondrogenesis [184]
Osteogenesis imperfecta [47]
Thanatophoric dysplasia [185]
Asphyxiating thoracic dystrophy (Jeune) syndrome (11)
Saldino–Noonan syndrome [186]
Greenberg dysplasia [187]
Desbuquois dysplasia type 1 [188]
Congenital cortical hyperostosis (Caffey disease) [189]
Neu–Laxova syndrome [47]
Multiple pterygium syndrome [47]
Fetal akinesia deformation sequence (Pena-Shokeir, type l phenotype) [47]
Myotonic dystrophy [102]
Myopathy with muscle spindle excess [190]
Amniotic bands [47]

Congenital tumors
Rhabdomyoma and tuberous sclerosis [191]
Pericardial teratoma [192]
Sacrococcygeal [193]
Congenital peribronchial myofibroblastic tumor [194]
Neuroblastoma [195]
Wilms' tumour [196]
Malignant rhabdoid Tumor (abdominal, kidney) [197, 198]
Hepatoblastoma [199]
Hepatic mesenchymal hamartoma [200]
Glioblastoma multiforme [201]
Congenital leukemia, Down syndrome [202, 203]
Kaposiform hemangioendothelioma [204]
Congenital fibrosarcoma [205]
Mesoblastic nephroma [178]

Intrathoracic abnormalities
Pulmonary agenesis [171]
Tracheobronchomalacia [172]
Adenomatoid malformation [43, 44]
Pulmonary sequestration [43, 55]
Laryngeal or Tracheal atresia [44, 71]
Mainstem bronchial atresia [173]
Mesenchymal hamartoma [174]
Diaphragmatic hernia [43, 44]
Accessory diaphragm [175]

Urogenital abnormalities
Renal hypoplasia [44]
Fraser syndrome [177]
Autosomal recessive kidney disorder [178]
Mesoblastic nephroma [179]
Bartter syndrome and unilateral ectopic renal cyst [180]
Congenital nephrotic syndrome [181]
Urethral obstruction [44]
Vaginal atresia, hydrometrocolopos syndrome [47]
Cystic malformation of the lower femal genital tract [182]
Fetal gonadoblastoid testicular dysplasia [183]

Other fetal anomalies
Hyperthyroidism [206]
Incontinentia pigmenti [207]
Simpson–Golabi–Behmel syndrome [208]

Central nervous system abnormalities
Hydrocephaly, arthrogryposis [45]
Holoprosencephaly [72]
CNS destruction, hypomobility [209]

Placenta
Chorioangioma [210, 211]
Placental mesenchymal dysplasia [212]
Abnormal course of umbilical vein [93]
Umbilical cord torsion [213]
Choriocarcinoma [131]

Maternal disorders
Maternal lupus anticoagulant,fetal renal vein thrombosis [214]
Rheumatological disorders [48, 215]

Multiple pregnancy
Acardiac monozygous twin pregnancy [43]
Fetofetal hemorrhage (twin-transfusion syndrome) [44]

Table 13.3 Common diseases and the underlying mechanisms leading to fluid accumulation

Common diseases associated with fetal hydrops	Mechanisms leading to fetal hydrops
Hematologic	
Rh incompatibility/isoimmunisation	Hemolytic anemia due to incompatibility of maternal and fetal blood type
Down syndrome Red blood cell aplasia: parvovirus B19 Dyserythropoiesis Hemoglobinopathies: alpha thalassemia, G6P dehydrogenase def.	Nonimmune fetal anemia due to abnormal hematopoiesis
Feto-maternal hemorrhage Hemorrhage into fetal organs or fetal tumors Feto-fetal hemorrhage: TTTS	Non-immune fetal anemia (and tissue hypoxia) due to fetal blood loss
Kasabach Merritt syndrome	Increased destruction
Cardiovascular disease	
Congenital heart malformation	Increased right atrial pressure and/or volume overload, due to structural abnormality
Intracardiac tumor	Obstructed blood flow within the heart
Cardiomyopathy, incl. mitochondrial disorder Myocarditis Myocardial infarction	Cardiomyocyte dysfunction and reduced myocardial compliance
Tachyarrhythmia: supraventricular tachycardia, Wolff-Parkinson White syndrome	Inadequate diastolic ventricular filling, reduced cardiac output
Atrioventricular block due to: Maternal SLE Inherited progressive cardiac conduction disorder Congenital heart disease e.g. left atrial isomerism, discordant AV connection	Immune-mediated atrioventricular block due to transplacental passage of maternal anti-SSA/Ro-SSB/La antibodies
Lymphatic dysplasia Congenital pulmonary lymphangiectasia	Reduced lymphatic drainage and return to the heart
Fistulas and vascular malformations	High cardiac output failure due to “vascular steal phenomenon”
Arterial calcification	
Pulmonary and thoracic abnormalities	
Intrathoracic SOL e.g. CPAM, sequestration, CDH Pleural fluid Chylothorax	Reduced systemic venous return to right atrium due to increased intrathoracic pressure and external compression of heart and great vessels
Neuromuscular disease	Restricted chest movements
Congenital high airway obstruction syndrome	Reduced fetal swallowing of amniotic fluid Bilateral hyperinflated lungs leading to increased intrathoracic pressure obstructing venous return to heart
Chromosomal and single gene diseases	
Turner syndrome/Monosomy X	Impaired lymphatic drainage due to lymphatic malformation Cardiac failure due to cardiac malformation
Down syndrome	Transient abnormal myelopoiesis leading to anemia Cardiac failure due to cardiac malformation Lymphatic dysplasia
T18, T13, Triploidy	Cardiac failure due to cardiac malformation
Noonan syndrome (RASopathy)	Cardiac failure due to cardiac malformation
Skeletal dysplasia	Small chest with increased intrathoracic pressure
Inborn error of metabolism: lysosomal storage disease, congenital disorders of glycosylation [131]	Cardiac failure due to cardiomyopathy Increased metabolic demand leading to high output cardiac failure Hepatomegaly, compression of the sinusoids leading to reduced venous return to the heart Reduced liver function causing hypoproteinemia and decreased plasma oncotic pressure Bone marrow infiltration by storage cells
Other organ systems	
Neuromuscular disease e.g. myotonic dystrophy Esophageal atresia	Reduced swallowing of amniotic fluid leading to polyhydramnios
Intraabdominal SOL: tumor, cystic kidneys, enlarged urinary bladder Volvulus Hepatomegaly	External compression of abdominal great vessels resulting in increased hydrostatic pressure in the capillaries and reduced venous return to the heart

(continued)

Table 13.3 (continued)

Common diseases associated with fetal hydrops	Mechanisms leading to fetal hydrops
Congenital nephrotic syndrome	Renal protein loss/hypoproteinemia
Renal ischemia Renal vein thrombosis	Renal tubular damage or thrombosis leading to excess urine production
Infections	
TORCHS	Increased capillary permeability due to damage to endothelial cells Liver destruction reduced hepatic function, leading to reduced protein production/ hypoproteinemia
Coxsackie, adenovirus	Cardiac failure due to myocarditis and arrhythmia
Parvovirus B19	Anemia (and tissue hypoxia) due to red blood cell aplasia/hemolytic anemia Myocarditis
Congenital tumor Teratoma Neuroblastoma Lymphangiomas	External compression of abdominal great vessels resulting in increased hydrostatic pressure in the capillaries and reduced venous return to the heart High cardiac output failure due to shunting of blood flow through tumors "vascular steal phenomenon", and increased metabolic increase due to rapid tumor growth Bone marrow infiltration replacing bone marrow Intramural hemorrhage leading to fetal anemia/hypoxia
Placenta	
Hypercoiled cord	Umbilical vascular compression
Chorangioma	Fetal anemia due to transplacental hemorrhage
Twin to twin transfusion syndrome	Arteriovenous anastomosis with monochorionic placenta: anemia, hypoproteinemia and ventricular failure in donor twin polycythemia and hypervolemia in recipient twin
Maternal diseases	
Maternal SLE	Complete heart block

CDH congenital diaphragmatic hernia; *CPAM* congenital pulmonary airway malformation; *DA* ductus arteriosus; *FO* foramen ovale; *IEM* inborn error of metabolism; *SLE* systemic lupus erythematosus; *SOL* space occupying lesion; *TORCHS* toxoplasmosis, others, rubella, cytomegalovirus, herpes, syphilis; *TTTS* twin to twin transfusion syndrome

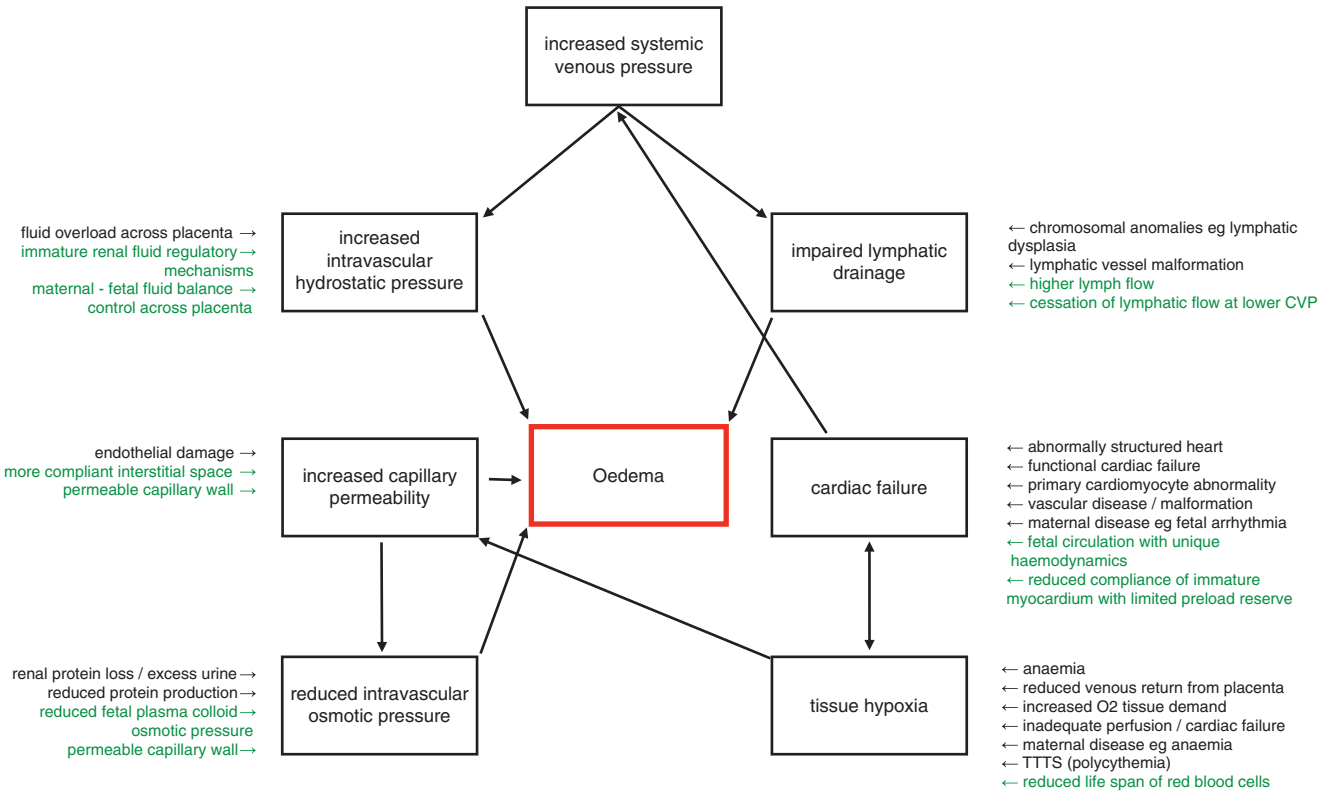

Fig. 13.1 Mechanisms of fetal edema with contributory fetal physiological factors (in green)

Table 13.4 Categories of non-immune fetal hydrops

Study	Idiopathic	Cardiovascular	Chromosomal	Genetic, incl. IEM	Hematological	Infection	Syndromic (non-chromosomal)	Thoracic, GI and liver	Urogenital	Lymphatic dysplasia, chylothorax, hygroma	Other
Bellini et al. (2009) [1]	17.8%	21.7%	13.4%	1.1%	10.4%	6.7%	4.4%	6.5%	2.3%	5.7%	10%
Takci et al. (2014) [9]	29.4%	11.8%	2.9%	8.8%	8.8%	2.9%				23.6%	11.8%
Bellini (2015) [216]	19.8%	20.1%	9.0%	1.3%	9.3%	7.0%	5.5%	3.6%	0.9%	15.0%	8.2%
Yeom et al. (2015) [14]	30.6% (13/42)	23.8% (10/42)	7.1% (3/42)	2.4% (1/42)		7.1% (3/42)	9.5% (4/42)	4.8% (2/42)			14.3% (6/42)
Ota et al. (2016) [15]	13% (12/92)	17.4% (16/92)	27.2% (25/92)			8.7% (8/92)	6.5% (6/92)	2.2% (2/92)	1.1% (1/92)	16.3% (15/92)	7.6% (7/92)
He et al. (2017) [16]	13.1%	6.4%	13.5%		61.8% (Bart's hydrops)	1.5%		1.6%		0.6%	1.2%
Laterre et al. (2018)[a] [217]	13.7%	9.8%	32.4%		7.8%	7.8%	9.8%	2.0%	1.0%	13.7%	2%
Gilby et al. (2018) [17]	31%	21%					19%	14%			
McPherson (2019)[b] [218]	37%	5.8%	29%	0.35%	3.6%	2.8%	14%	0.7%	1.4%		4.6%

IEM inborn error of metabolism; *GI* gastro-intestinal

[a]Intestinal lymphangiectasia was included in "lymphatic dysplasia" category in this study

[b]Most of the fetuses had no histological examination in this study and idiopathic cases were not investigated for lymphatic dysplasia [218]

13.6.1 Cardiovascular Disease

Physiology of fetal circulation is unique. In the fetal heart, left and right ventricular circulations are connected via foramen ovale and ductus arteriosus. The fetal myocardium is structurally and functionally immature, relatively stiff with reduced relaxation capacity, and has limited preload reserve. Therefore, the developing fetal heart can only increase cardiac output by increasing its heart rate [219]. Antenatally, the right ventricle is the dominant and is sensitive to afterload changes in the systemic arterial circulation.

In right ventricular failure, diastolic emptying is reduced with resultant increase in end diastolic pressure and volume load in the right atrium. In left ventricular failure, left atrial filling from the inferior vena cava via the foramen ovale is reduced with similar hemodynamic consequences as seen in right ventricular failure. Increased pressure in the systemic venous circulation increases the hydrostatic intravascular pressure at the capillary level in the tissues leading to fluid loss across the capillary wall and serous surfaces [220].

When the heart is abnormally structured, it can cause altered blood flow through the heart and the connected large vessels, depending on the malformation. Foramen ovale and ductus arteriosus might provide alternative pathways for the blood flow in the events of obstruction. Cardiomyocyte dysfunction, either due to hypoxia, inflammation or other primary disease (e.g. cardiomyopathy), is another possible cause of cardiac failure. Tachyarrhythmia, including supraventricular tachycardia and fetal atrial fibrillation, reduces diastolic filling and therefore, reduces cardiac output. Bradyarryhthmia is most commonly due to congenital heart block (e.g. maternal systemic lupus erythematosus) and structural abnormality (e.g. left atrial isomerism). Reduced cardiac function results in inadequate tissue perfusion and tissue hypoxia further exacerbates the developing hydrops [24].

Lymphatic malformations, including cystic hygromas, are associated with abnormal lymphatic development, resulting in defective lymphatic drainage of the tissues and reduced lymphatic return to the heart. Bellini et al. demonstrated abnormal lymphatic channels in 21.5% of the idiopathic non-immune hydrops cases [221]. Many studies have demonstrated the relationship between mutations involving vascular endothelial growth factor receptors (VEGFR), RAS/MAPK, P13K/AKT and NK-kB signaling pathways and NIFH [222]. Ghalamkarpour et al. reported mutations in *VEGFR3* and *FOXC2* genes in cases with hydrops fetalis, and advised to get these lymphangiogenic genes tested in idiopathic NIFH [223].

13.6.2 Chromosomal and Genetic Abnormality

Chromosomal aneuploidies and single gene diseases commonly cause various structural abnormalities and are difficult to assign these diseases into one organ system category. For example, congenital heart malformation and lymphatic dysplasia are commonly found in fetuses with Down syndrome, both of which could be the underlying pathophysiological mechanisms of fetal hydrops. Moreover, approximately 30% of cases with prenatal transient abnormal myelopoiesis (TAM), which is another frequently seen disease with Down syndrome [150], have fetal hydrops on ultrasound examination [224]. Prenatal TAM presents most commonly in the third trimester and 71.8% of the cases have at least two ultrasound features of the following findings: fetal hydrops, pericardial effusion, pleural effusion, ascites, peripheral edema, abnormal amniotic fluid volume, cardiac abnormalities, hepatomegaly and splenomegaly [224].

A particular constellation of the structural abnormalities may provide clues about the underlying chromosomal or genetic abnormalities. For example, cardiac rhabdomyoma is associated with tuberous sclerosis and cardiomyopathies are seen in lysosomal storage disorders and RASopathies. There are increasing number of single gene disorders associated with fetal hydrops which affect metabolic pathways, hematological conditions, skeletal dysplasia, neuromuscular diseases, mitochondrial disorders, cardiomyopathies, congenital nephrosis and congenital lymphedema. Specific enzyme assays on cultured amniocytes, measurement of specific metabolites in amniotic fluid and antenatal genetic testing are available means to aid diagnosis of these diseases.

13.6.3 Anemia

Immune fetal hydrops is due to a maternal immunological response to paternally inherited antigens present on red blood cells. Hemolytic anemia has been associated with more than 60 different red cell antibodies of which rhesus D, C, c and E are the commonest. Trans-placental passage of maternal IgG class antibodies results in immune hemolysis of fetal red blood cells. IgM usually results in mild hemolysis [225]. Fetal hydrops is secondary to fetal anemia and high output cardiac failure.

Causes of non-alloimmune anemia include deficient production of red blood cells, hemolysis, and hemorrhage. In these conditions, the fetus has a higher risk of developing anemia as the life span of fetal erythroid cells is shorter than in adults [226]. Reduced mature red blood cell production may be due to constitutional hematological diseases (e.g.

hemoglobinopathies and erythrocyte enzyme deficiencies), bone marrow infiltration or reduction of bone marrow spaces (e.g. skeletal dysplasia). Aplasia of the erythroid precursors is seen in parvovirus B19 infection. Thalassemia is a frequent cause of hydrops in Thailand and in nearby parts of the world [6]. Increased destruction of the erythroid elements can be secondary to constitutional disease. Fetal onset of familial hemophagocytic lymphohistiocytosis is extremely rare but remains a possible cause of anemia [152]. Anemia may cause tissue hypoxia compromising cardiac, hepatic and renal function (e.g. renal tubular damage, endothelial damage, cardiomyocyte ischemia) and high output cardiac failure, further contributing to progressive edema formation.

13.6.4 Intrauterine Infection

Fetal hydrops can be a serious manifestation of intrauterine infection. To date, numerous infective organisms have been described with fetal hydrops. Infection causes tissue injury, such as severe liver destruction (e.g. HSV, syphilis) resulting in reduced protein synthesis, myocarditis (e.g. coxsackie, adenovirus) leading to arrhythmias, and endothelial cell damage with leaking capillaries. Parvovirus B19 infects erythroid precursors and fetal myocardium; it has a direct toxic effect on the cells and induces apoptosis, leading to red blood cell aplasia and hemolytic anemia, and myocarditis [227].

13.6.5 Other Organ Systems

Thoracic, gastrointestinal, and urogenital abnormalities are well-recognised but rare associations with hydrops. These can act as space occupying lesions and compress great vessels. This results in increased hydrostatic pressure in the capillaries and reduced venous return to the heart. Reduced swallowing either due to neuromuscular disease or atresia reduced amniotic fluid reabsorption, leading to polyhydramnios.

Many central nervous system anomalies may be seen with fetal hydrops in the setting of an underlying genetic disease. In these cases, brain abnormalities are not thought to be causative of hydrops but represent a manifestation of the underlying etiology leading to hydrops [226].

Various congenital tumors have been described in association with hydrops (Table 13.2) and they can cause fetal hydrops by many mechanisms. These include external compression of great vessels resulting in increased hydrostatic pressure in the capillaries and reduced venous return to the heart (e.g. intrathoracic or intrabadominal tumors), high output cardiac failure due to shunting of blood flow through highly vascularized tumors ("vascular steal phenomenon") or due to increased metabolic rate of a rapidly growing tumor, fetal anemia to the intratumoral hemorrhage and reduced hematopoiesis in the bone marrow due to tumor infiltration. Lymphangiomas/lymphatic malformations might be associated with hypoproteinemia, and neuroblastoma can produce catecholamine further contributing to cardiac failure (i.e. catecholamine cardiomyopathy). Some of these malignancies can also metastasize to the placenta.

The majority of inborn errors of metabolism, associated with fetal hydrops, are lysosomal storage diseases (LSD). Al-Kouatly et al. demonstrated that the most common LSD in NIFH are galactosialidosis, sialic acid storage disease, mucopolysaccharidosis VII, and Gaucher disease [228].

13.6.6 Placenta, Multiple Pregnancies, Maternal Disease

Maternal - fetal fluid exchange occurs in the placenta; therefore, the placenta has an essential role in fetal fluid balance (see *Amniotic fluid* above).

Abnormal placental circulation, such as increased placental vascular resistance, can lead to cardiac failure and contribute to fluid accumulation in the fetal compartments. Reduced blood return from the placenta (e.g. umbilical cord lesions, hypercoiled cord, intra-abdominal masses obstructing the umbilical vessels) decreases oxygen and nutrient supply to the fetal tissues (i.e. tissue hypoxia), compromising organ function. Hemorrhage into chorangiomas leads to fetal anemia.

In multiple pregnancies, twin-to-twin transfusion syndrome (TTTS) is the most common cause of fetal hydrops, which could involve both twins. The donor twin develops severe anemia, hypoproteinemia and ventricular failure, and the recipient twin develops polycythemia and hypervolemia.

Maternal antibodies against fetal red blood cells cross the placenta and result in hemolytic anemia (immune hydrops). In maternal systemic lupus erythematosus, maternal antibodies (anti-Ro and anti-La) cause damage to the heart conductive system resulting in congenital fetal heart block.

13.7 Investigation of Fetal Hydrops

The aims of antenatal investigations are to ascertain the underlying cause of fetal hydrops, to facilitate decision making with regard to patient management and to support further genetic counseling of the family. Moreover, these tests can demonstrate the severity of fetal edema, the degree of polyhydramnios and the extent of placental involvement [45]. Antenatal and postnatal investigations completed with postmortem examination are the best combination to reach a final diagnosis (>90%) [229] (Tables 13.5 and 13.6).

Table 13.5 Antenatal investigation of mother and hydropic fetus

Maternal investigation	Fetal investigation
Clinical evaluation	Blood sample
Blood sample	Blood cell count, including platelets
Blood cell count	Blood group and type
Blood group and antigen status	Hb level
Indirect Coombs	Direct Coombs' test
Kleihauer-Betke test/flow cytometry	Metabolic investigations
Autoantibody screen (anti SSA/SSB)	Serology TORCHS screen
Serology TORCHS screen	Hb electrophoresis (depending on ethnicity)
Coagulation tests	Karyotype (QF-PCR, FISH)
Depending on ethnic origin: Hb electrophoresis,	Amniotic fluid (or CVS)
Erythrocyte enzymes (e.g. G6PD)	Chromosomal analysis: FISH or QF-PCR, karyotype or aCGH (microarray)
Chromosome analysis	Single gene analysis
Ultrasonography	PCR for viruses and parasites (e.g. CMV, parvovirus B19)
Amniotic fluid index	Viral and bacterial cultures
Placental morphology	DNA extraction (alpha thalassemia)
Doppler	Biochemical studies (lung maturation)
	Imaging
	Detailed anomaly scan
	Fetal echocardiography
	Doppler (MCA, venous, arterial)
	Specific enzyme assays (fetal blood, amniotic fluid)
	Lysosomal enzymatic assays

AFP alpha fetoprotein; *CVS* chorionic villous sampling; *Hb* hemoglobin; *TORCHS* toxoplasmosis other rubella cytomegalovirus, herpes simplex, syphilis. Modified from Refs. [226, 230, 231]

Table 13.6 Postnatal investigation of hydropic neonate

At birth	At necropsy
Review of prenatal results (Table 13.5)	Review of prenatal results
Physical examination and measurements	Skin/placenta for fibroblast culture
Blood sample	Chromosomal analysis
Blood cell count	Enzyme assays
Liver function test, creatine kinase, albumin, protein	Storage of fetal DNA
Clotting screen	Photographic documentation of external and internal findings
Infection screening (TORCHS, viral culture)	Skeletal survey (Faxitron)
Imaging	Detailed external and internal examination of the fetus, including measurements, organ weights, histology of main organs[a]
Echocardiography	Examination of the placenta
Cardiac monitoring	Ancillary investigation:
Ultrasonography (cranial, abdominal)	Bacterial and viral cultures, PCR
Other radiological examinations	Bone histology (skeletal dysplasia)
	Skeletal muscle (neuromuscular disease)
	Electron microscopy (CMP, neuromuscular disease, ciliopathies)
	Snap frozen tissue storage (e.g. spleen, liver) for future molecular analysis
	Snap frozen tissue (heart, liver, kidney, muscle) for ORO stain (IEM)

CMP cardiomyopathy, IEM inborn error of metabolism, ORO oil red O, TORCHS toxoplasmosis other rubella cytomegalovirus, herpes simplex, syphilis

[a]Body measurements may be unreliable in severe hydropic cases. Modified from Refs. [231–233]

The spectrum of genetic testing used in prenatal diagnosis has been expanded in recent years. Chromosomal microarray analysis detects chromosomal imbalances and is recommended as a first-line genetic diagnostic test for fetal anomalies. New molecular techniques, such as targeted-next generation sequencing and whole genome or exome sequencing are useful tools to identify or confirm the genetic cause in structural abnormalities, especially in cases with rare single gene mutations or in cases with non-specific phenotypic features, to detect new disease and to improve existing genotype - phenotype associations of already known Mendelian disorders (see Chaps. 3, 8). However, exome sequencing in prenatal diagnostic settings requires more cautious interpretation, as Aggarwal et al. [234] suggested, as information on phenotype in prenatal setting might not be complete and is obtained by ultrasound and other prenatal imaging. Postnatal and/or post mortem phenotype information should be correlated with antenatal findings.

13.7.1 Pathological Findings

In autopsy practice, the frequency of hydrops cases varies between 16% [6] and 6.07% [235] of stillborn cases and is 7.45% in neonatal death cases [236]. The most common cause was cardiovascular disease (50%) in neonatal/infant deaths [235, 236] and congenital infection (34%) in stillbirths [229].

13.7.1.1 External

The affected fetus is usually preterm and pale in appearance. There is soft tissue edema, the amount and distribution of which is variable. The head and face are often markedly affected, obliterating dysmorphic features or producing changes, such as ear folding, mimicking dysmorphism (Fig. 13.2). A disproportionate amount of postnuchal fluid accumulation is usually seen in monosomy X (Fig. 13.3a, b), although it is not specific for this condition and may occur with other chromosome abnormalities or with a normal karyotype. The ascites may cause abdominal distension (Fig. 13.4a). However, this could alternatively be secondary to hepatomegaly (Fig. 13.5). The limbs are sometimes spared without significant subcutaneous edema. There may be other external abnormalities or features apparent on the external examination e.g. skeletal dysplasia or extensive angiomata (Fig. 13.6), indicating the underlying causes of the hydropic state.

Postmortem X-ray examination of the fetus is useful for multiple reasons. It confirms soft tissue shadowing of the expanded edematous tissue (Fig. 13.7), detects abnormalities of bone mineralisation and development (skeletal dysplasia) and shows internal organ calcification (congenital infection).

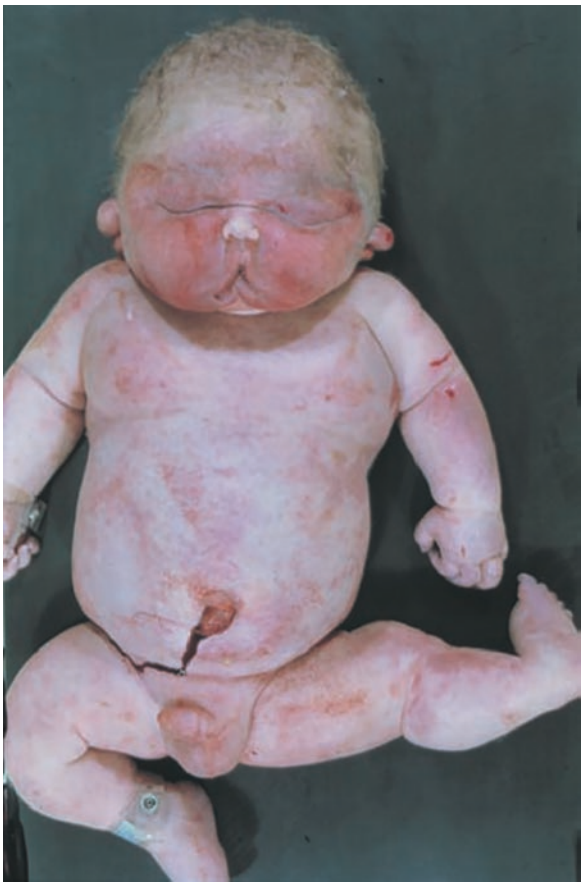

Fig. 13.2 Pale fetus with generalized subcutaneous edema of the head, trunk and limbs. Facial deformity secondary to edema

If consent for a full autopsy is not available, postmortem magnetic resonance imaging (MRI) is a non-invasive investigation that may be more acceptable to some families.

13.7.1.2 Internal

Postmortem examination of fetal hydrops should include a thorough systematic examination combined with ancillary investigations (Table 13.6) [232, 233]. This approach is most important in cases where an antenatal diagnosis has not been made or when all relevant examinations have not been completed satisfactorily. Complex malformation syndromes can be technically very challenging and further complicated by secondary changes of maceration or the small size of the fetuses.

Upon opening the body cavities, serous fluid collections should be sought, recorded, and measured, if possible. Excess of serous fluid is found in all body cavities in most of the cases, although not usually to the same degree. Sometimes, there is disproportionate ascites and it is likely that in some, if not many of these babies, ascites accumulates first and hydrops follows because elevated intra-abdominal pressure distorts the umbilical vein and impedes venous return from the placenta. Machin et al. [237] studied cases with fetal ascites and found that many of the cases were associated with generalized hydrops. Moreover, it was also found that more cases were associated with intra-abdominal abnormalities such as urinary tract obstruction and gastrointestinal or hepatic abnormalities. Large amount of pericardial effusion is unusual, unless there is intrapericardial pathology

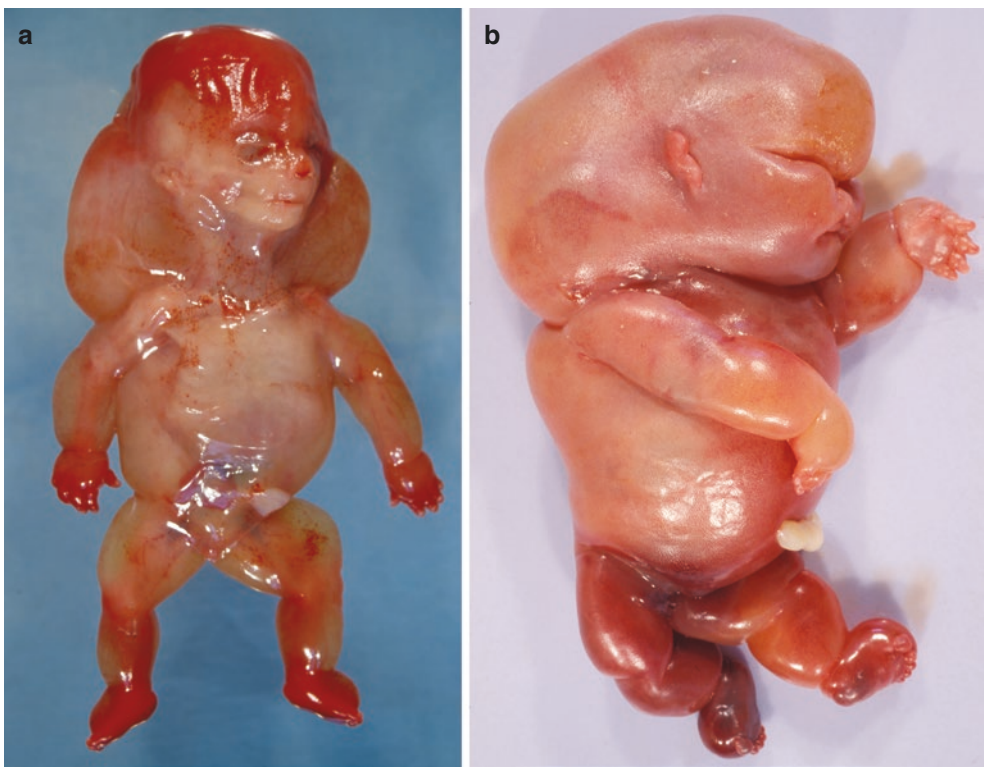

Fig. 13.3 (**a**) 45XO fetus with generalized subcutaneous edema and marked nuchal expansion. (**b**) Another 45XO fetus, later gestation, with generalized edema extending onto the hands and feet. Note the anterior displacement of the ear by the nuchal edema fluid

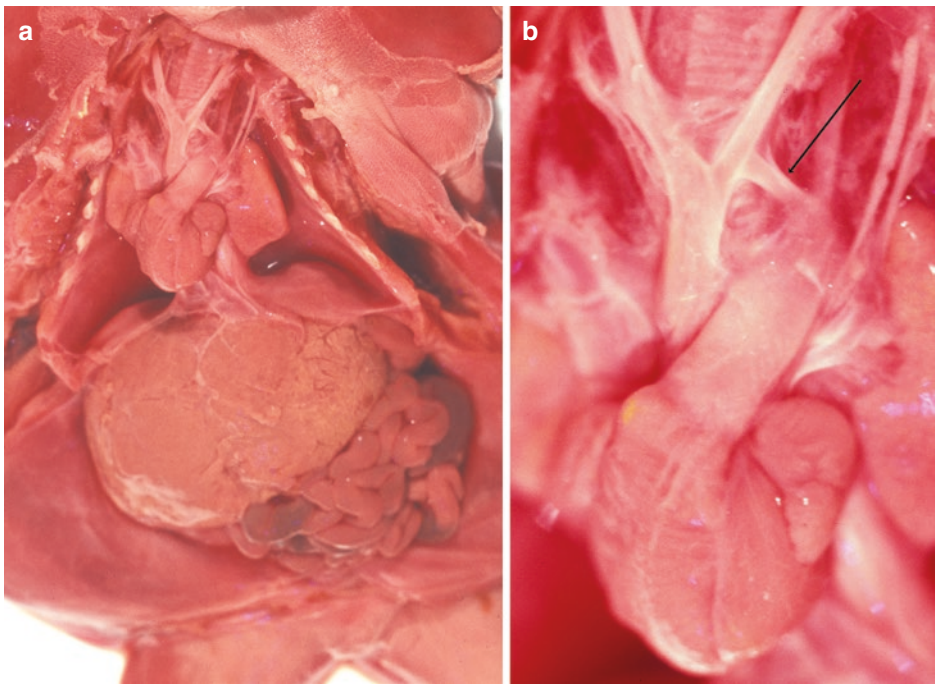

Fig. 13.4 (**a**) Hydropic fetus with 45XO karyotype. The pleural and peritoneal cavities are expanded due to serous fluid accumulation, compressing the lungs and intestines. (**b**) The pulmonary trunk is larger than the ascending aorta; the distal part of the aortic arch is very narrow (tubular hypoplasia)

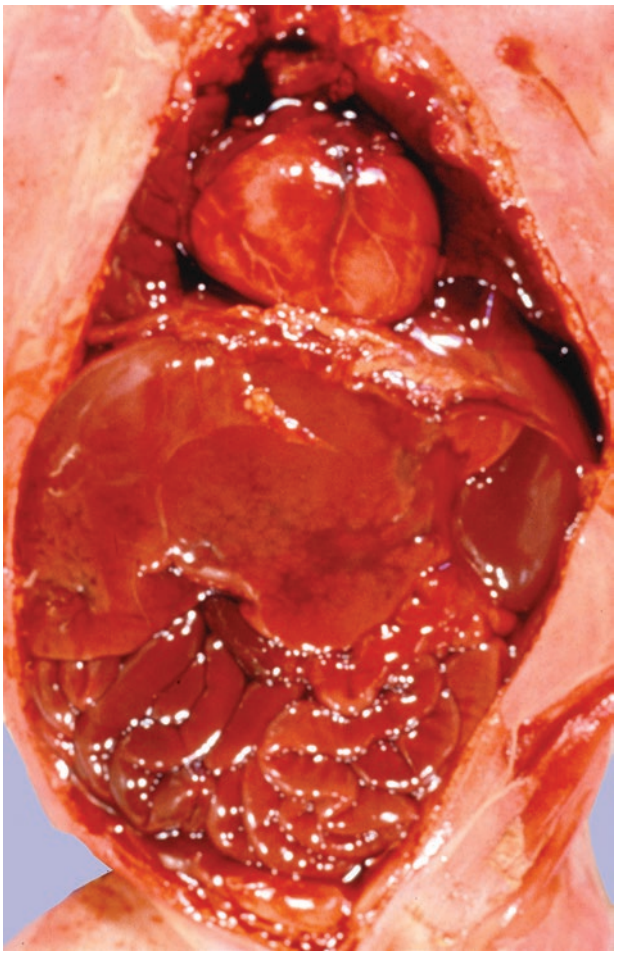

Fig. 13.5 Fetal hydrops due to severe rhesus incompatibility. Massive hepatosplenomegaly is the result of increased erythropoiesis

such as cardiac teratoma [192] (Fig. 13.8), rhabdomyoma (Fig. 13.9) or cardiac diverticulum [81].

Mild subcutaneous edema is often observed in macerated babies. Similarly, postmortem fluid accumulation in serous body cavities has dark red color and could be distinguished from antemortem serous effusion. The pleural effusions of some duration cause some degree of pulmonary hypoplasia (Fig. 13.10) and changes of the lobar contour; there is loss of concavity of the inferior surface of the lower lobes and an acute angle of the inferior border.

Isolated intra-abdominal fluid accumulations may be secondary to ruptured bowel, bladder, renal pelvis, or cystic structures. These do not represent fetal hydrops but reflect other conditions.

Malformations are amongst the commonest causes of hydrops and should be specifically sought. Congenital heart malformations are common causes of fetal hydrops. Intrathoracic masses can cause direct compression on the heart and the large vessels. Lungs can be enlarged due to malformations, such as congenital pulmonary airway malformation (Fig. 13.11), sequestration or hamartomas (Fig. 13.12). Alternatively, the lungs are expanded secondary to upper airway obstruction or stenosis as seen in bronchial atresia (Fig. 13.13) and laryngeal stenosis (Fig. 13.14). Herniating abdominal organs (Fig. 13.15) reduce intrathoracic space and have a similar mass effect in the chest leading to mediastinal shift with compression of the contralateral lung and great vessels.

Intra-abdominal causes include tumors (Fig. 13.16), cystic kidneys, lower urinary tract obstruction with dilated bladder and genital organ malformation (e.g. hydrometrocolopos).

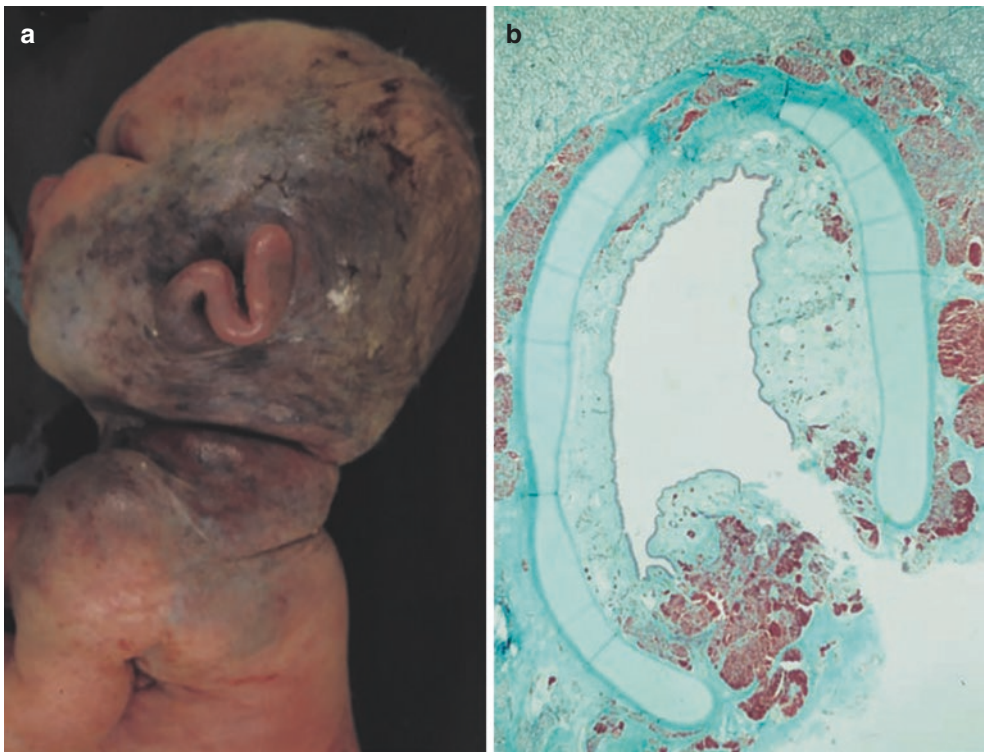

Fig. 13.6 (**a**) Hydropic stillbirth with a large angioma involving the left side of the face, head and shoulder. (**b**) The angioma involving the laryngeal mucosa and the surrounding soft tissue

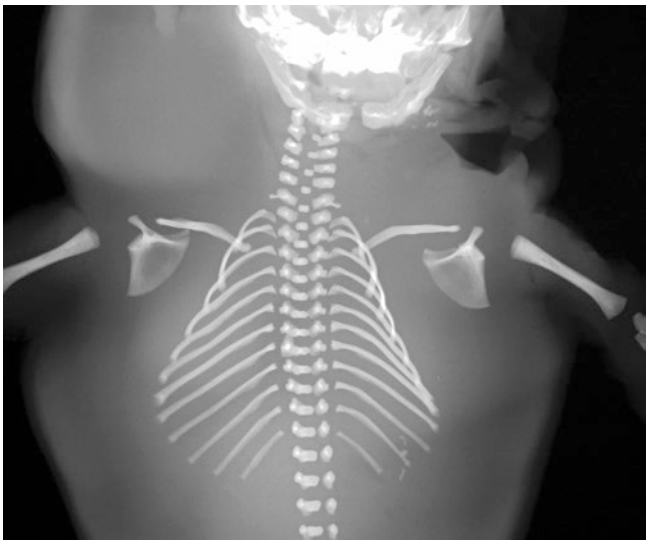

Fig. 13.7 Postmortem radiograph of a fetus with 45XO karyotype showing marked soft tissue expansion due to edema. Bilateral cervical ribs

Fig. 13.8 Cardiac teratoma arising from the root of the heart. Pericardial sac is markedly enlarged (upon opening was filled with serous fluid)

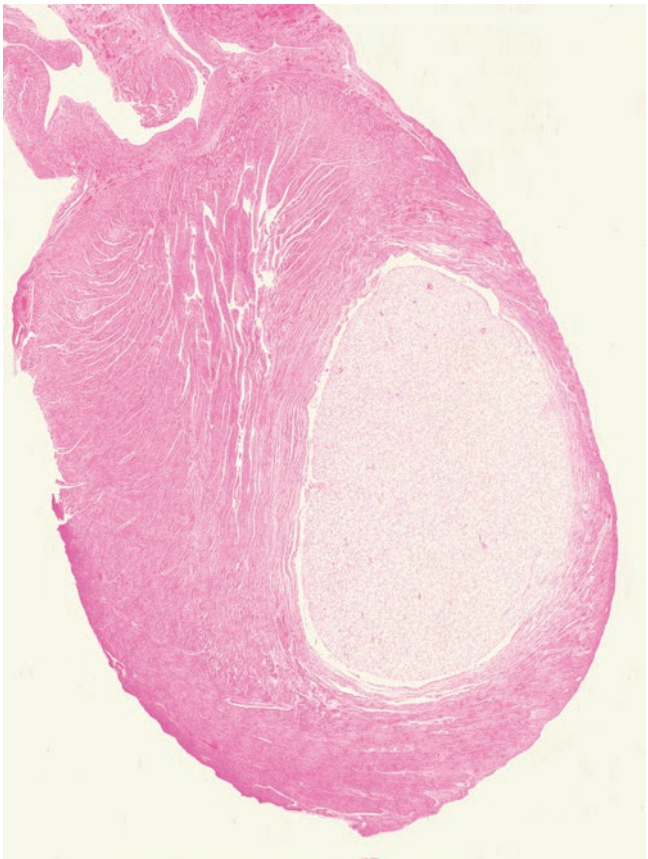

Fig. 13.9 Rhabdomyoma of the interventricular septum

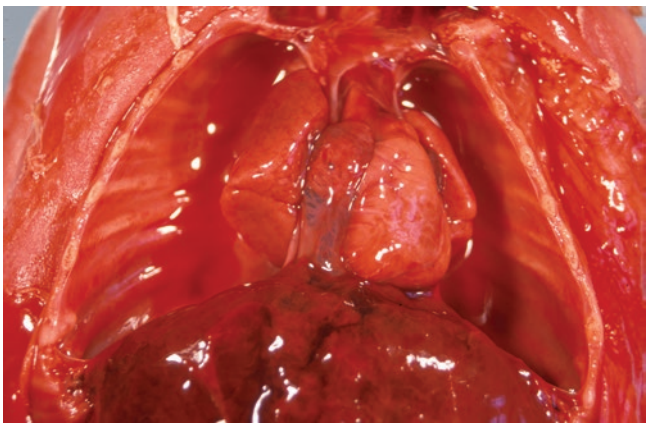

Fig. 13.10 Large bilateral pleural effusions with secondary severe pulmonary hypoplasia

Extramedullary hematopoiesis (EMH) can result in hepatomegaly. EMH develops as the result of intrauterine stress, fetal anemia (Fig. 13.5), hemorrhage, congenital infections, hypoxia and congenital defects [238], which all increase

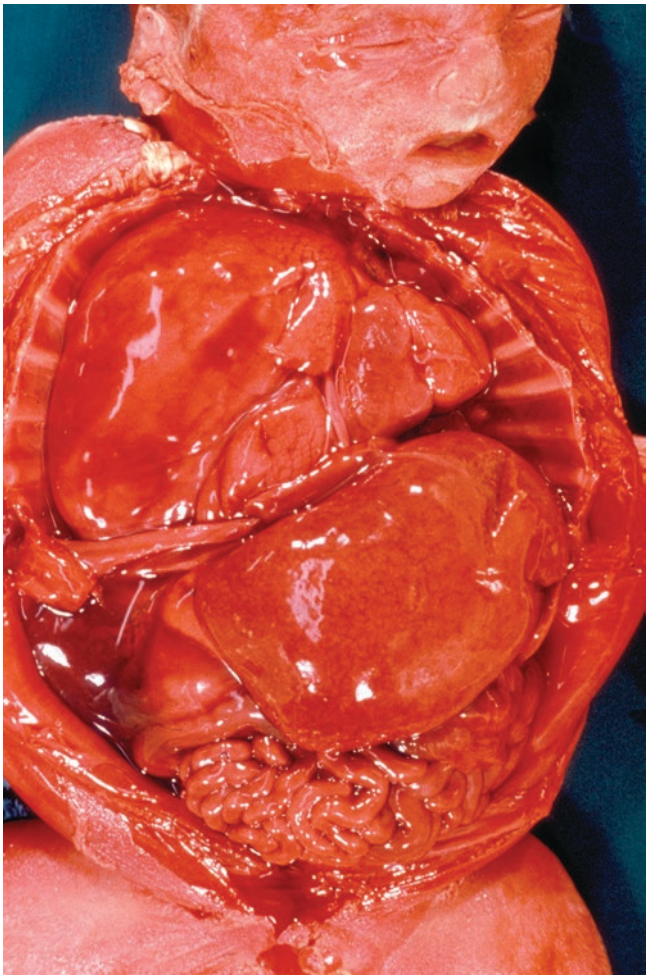

Fig. 13.11 Hydropic macerated stillbirth: congenital pulmonary airway malformation of right upper lobe of lung with mediastinal shift and displacement of the liver to the left. Right depressed hemidiaphragm

demand on bone marrow elements with resultant increased hematopoiesis. Alternatively, it is due to reduced bone marrow space in the bones, as seen in osteochondrodysplasias, or due to infiltrative lesions replacing the hemopoietic tissue for example in storage disease and familial hemophagocytic lymphohistiocytosis [151]. Intestinal pathology includes atresia and volvulus with hemorrhage and infarction. Sacrococcygeal teratomas can have a large intrapelvic component (Fig. 13.17).

Intracranial pathology includes congenital infections and tumors, vascular malformations and structural defects, presented with hydrocephalus, hemorrhage, necrosis and calcification (Fig. 13.18). Late disruptive defects, both intra- and extracranial, resulting from hypotensive ischemia or embolic phenomena should be sought in monochorionic twins [239].

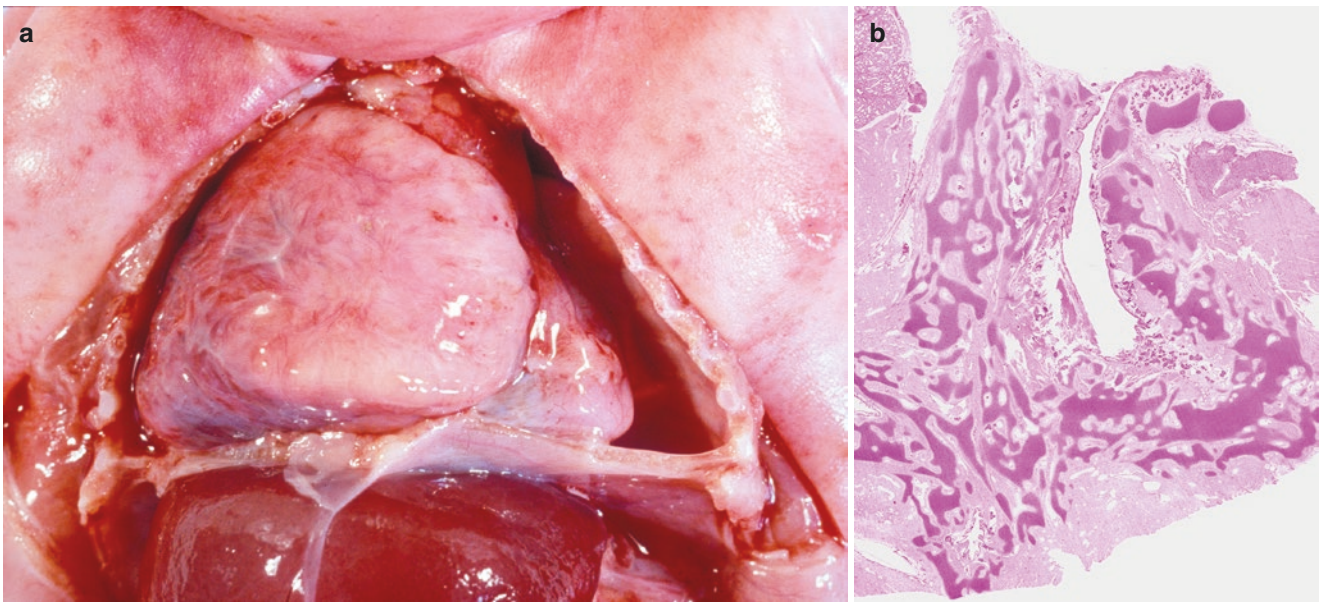

Fig. 13.12 (**a**) Mesenchymal hamartoma replacing the right upper lobe of the lung. (**b**) Hamartoma showing irregular bars of cartilage and myofibroblastic tissue

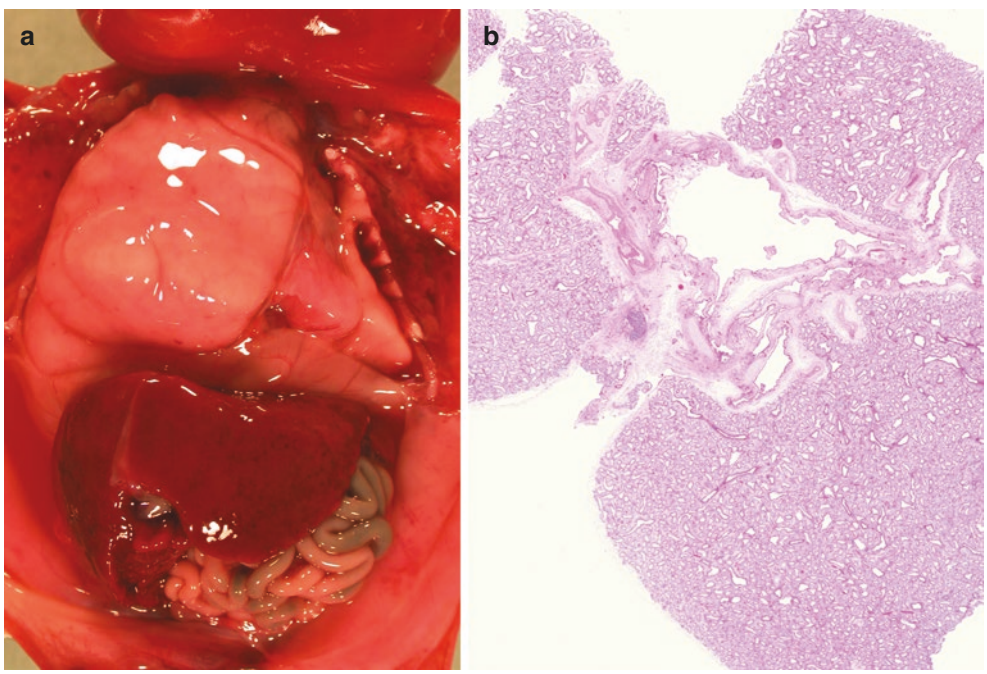

Fig. 13.13 (**a**) Expanded right middle and lower lobes of the lung due to bronchial atresia. Mediastinal shift and hypoplasia of the left upper and lower lobes and right upper lobe of the lung. (**b**) Dilated proximal bronchi with loss of the cartilage in their walls and with parenchymal hyperplasia

13.7.2 Histology

Routine sampling of organs for histological examination should be undertaken even when a gross abnormality thought to be causally related to the hydrops has been identified. Histological appearances of the heart and lungs may be particularly informative. The heart should be sampled initially in such a manner that the conduction system is undisturbed to allow subsequent detailed histological examination (Fig. 13.19). This may sometimes be informative in antena-

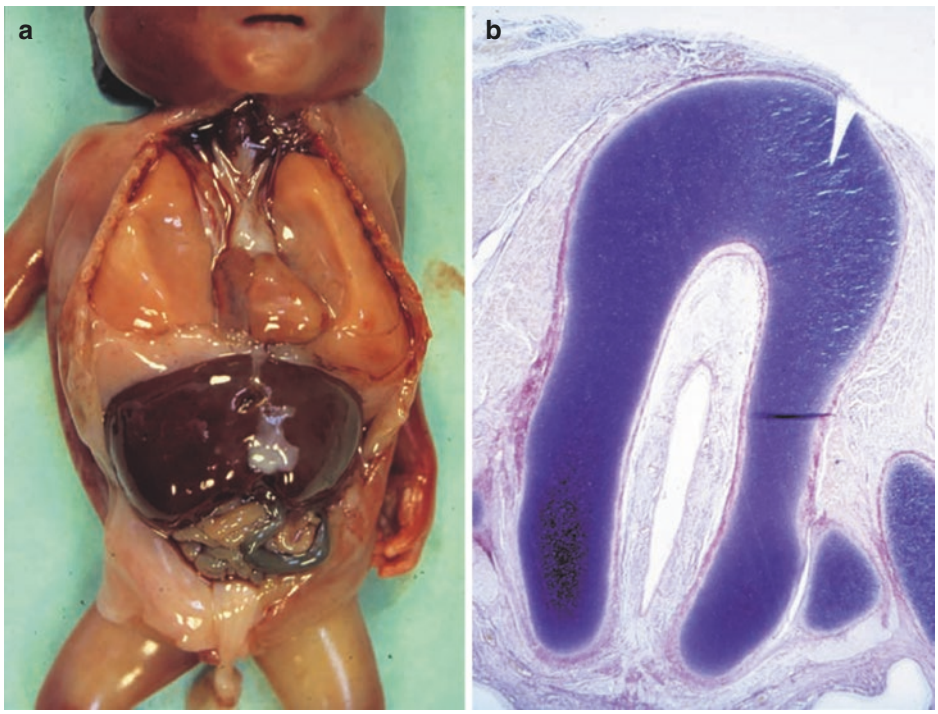

Fig. 13.14 (**a**) Fetus of 20 weeks' gestation. Massive distention of both lungs, depressing the diaphragm. (**b**) Severe laryngeal stenosis: anomalous development of the cartilaginous structures resulting in a slit-like lumen

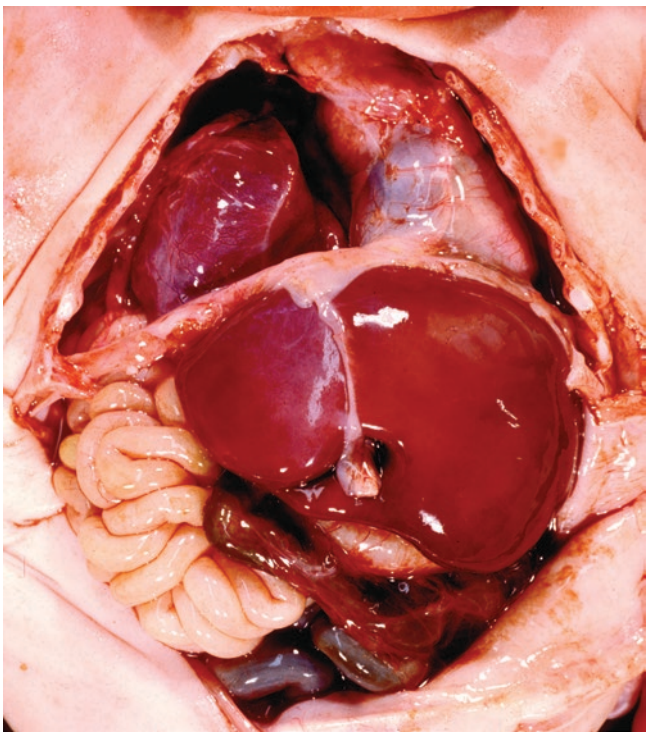

Fig. 13.15 Herniation of the right lobe of the liver via right-sided diaphragmatic defect into the right hemithorax, displacing the heart and lungs to the left and leading to fetal hydrops and polyhydramnios

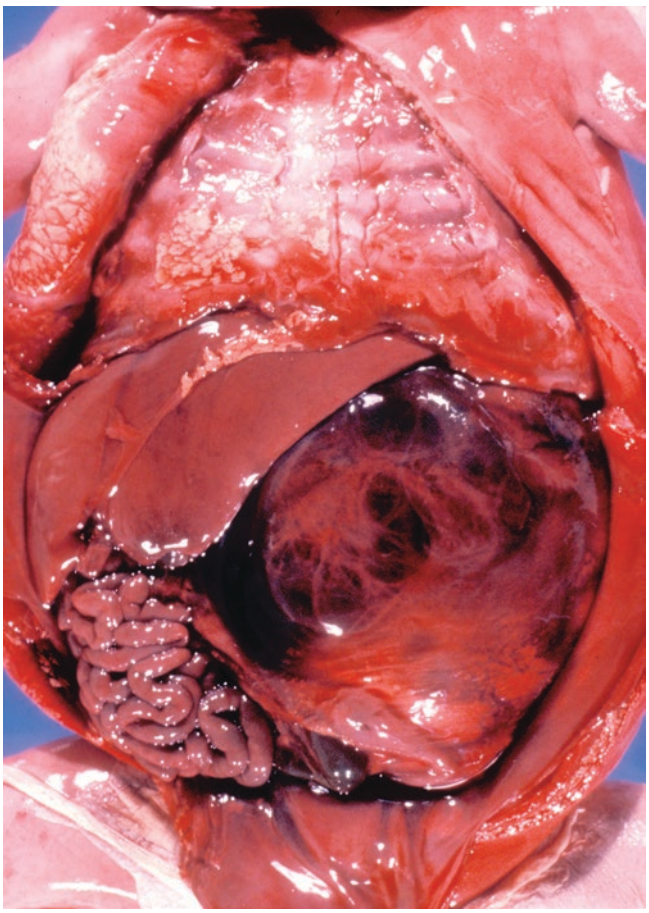

Fig. 13.16 Congenital mesoblastic nephroma of left kidney, displacing the intestines and the liver to the right and obstructing the systemic venous return leading to hydrops

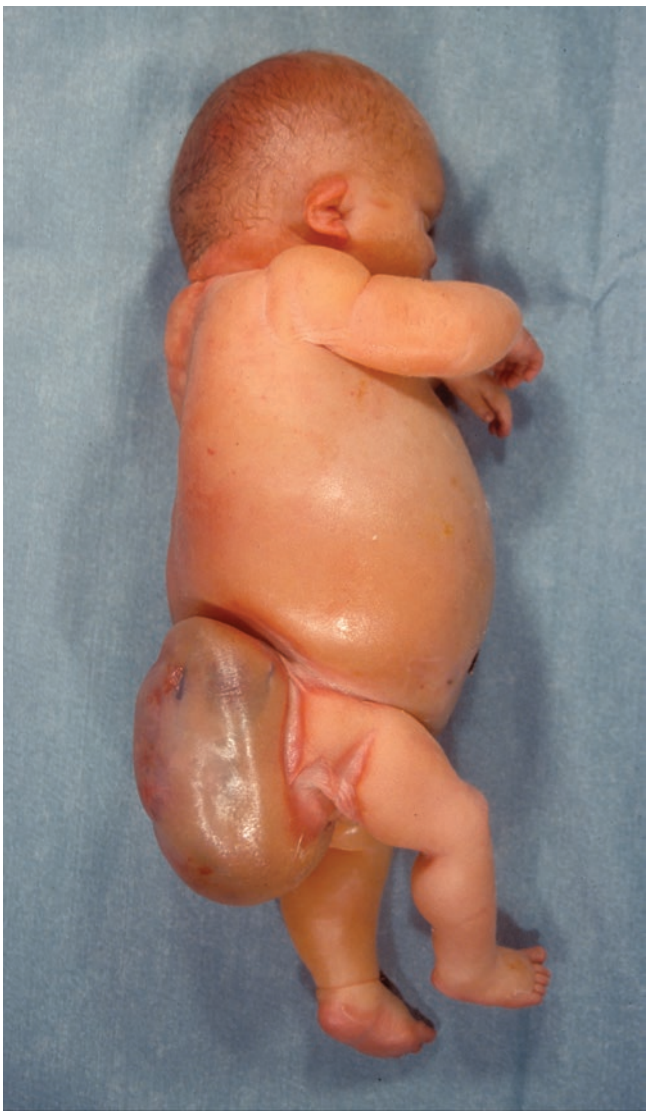

Fig. 13.17 Hydropic neonate with sacrococcygeal teratoma with a large intrapelvic component

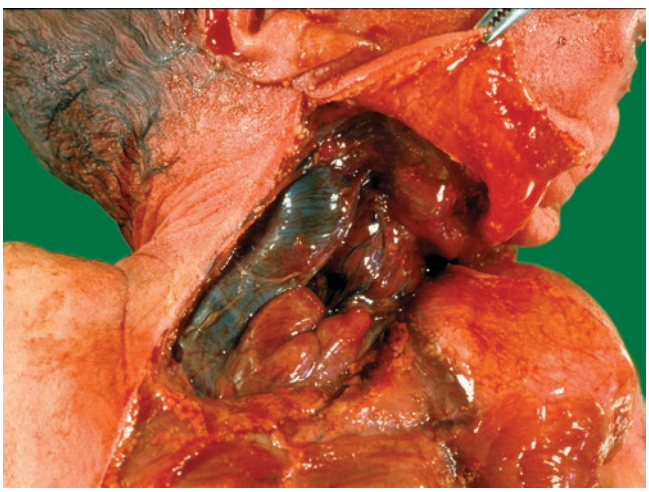

Fig. 13.18 Meningeal angiodysplasia leading to enlarged jugular vein (demonstrated on the photo) leading to high cardiac output

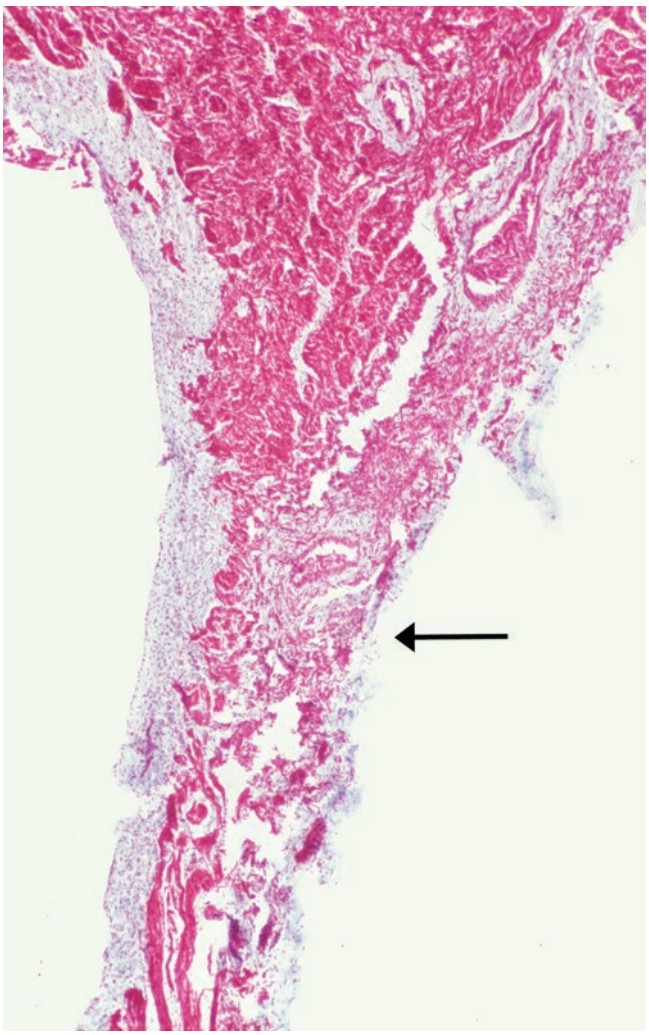

Fig. 13.19 Right atrial wall with a hypoplastic sinoatrial node (arrow) with a central sinus node artery (Masson's Trichrome stain)

tally detected fetal arrhythmias and in cases where there is a maternal history of systemic lupus erythematosus. In these cases, the AV node shows chronic inflammation, scarring and calcification. The myocardium may show myocarditis (e.g. parvovirus B19), infarction, calcification, fibrosis or vacuolation. Parasites (e.g. toxoplasma), in the absence of inflammatory tissue reaction, can easily be missed, especially in macerated fetuses.

Tumors may also be found, such as rhabdomyoma (Fig. 13.9). In such cases, other features of tuberous sclerosis should be sought. Various tumor types have been reported in association with hydrops. Soft tissue masses and lesions, either in the chest and/or in the abdominal cavity, should be examined. Histological examination of cystic lesions is important to distinguish hamartomata from other developmental abnormalities and neoplastic processes (e.g. cystic kidney disease).

In cases with a widened neck, it is advised to sample the posterolateral subcutaneous tissue for histological assessment.

Abnormal lymphatic vessels may be detected and confirmed with immunohistochemical stains (CD31, CD34, D2-40 or podoplanin, SMA, anti-LYVE-1 and VEGFR-3) [221, 240].

Adrenal glands may show adrenocortical cytomegaly, especially ones associated with Hb Bart hydrops fetalis [241]. Adrenocortical cytomegaly is a non-specific finding and may reflect a cellular adaptation to an intrauterine stressful environment. Therefore, it can be seen in various conditions, including congenital rubella infections and Beckwith-Wiedemann syndrome [23].

In certain situations, examination of the vessels may reveal the underlying cause (Fig. 13.20). Presence and distribution of soft tissue calcification on the X-ray examination may provide a guide to tissue sampling. Calcification can be seen in association with tissue necrosis (e.g. congenital infection) and with idiopathic calcification of the vessels and/or malformations.

Many viruses, e.g. CMV, Parvovirus B19, HSV, have characteristic intranuclear inclusions, which can be confirmed with immunohistochemical stains (Fig. 13.21).

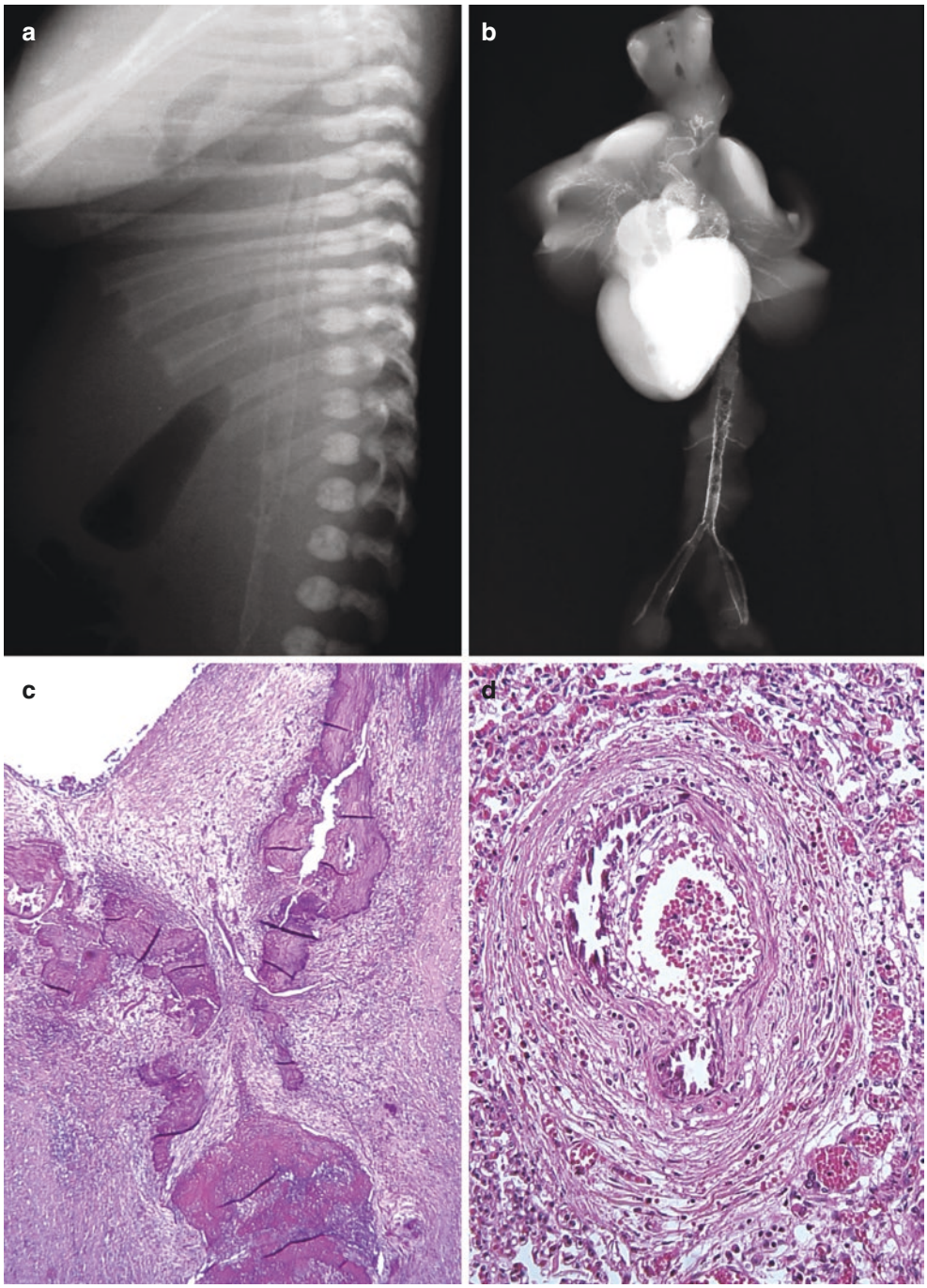

Fig. 13.20 (**a**) Lateral radiograph of a hydropic stillbirth with diffuse calcific arteriopathy. The aorta is outlined on the film owing to excessive mineralisation. (**b**) Postmortem radiograph of the dissected organ block (from a similar case) showing calcification within the pulmonary, renal and mesenteric arteries. (**c**) Heavily calcified proximal pulmonary arteries. (**d**) Mineral deposits partially replacing the internal elastic lamina, distal branches of pulmonary arteries

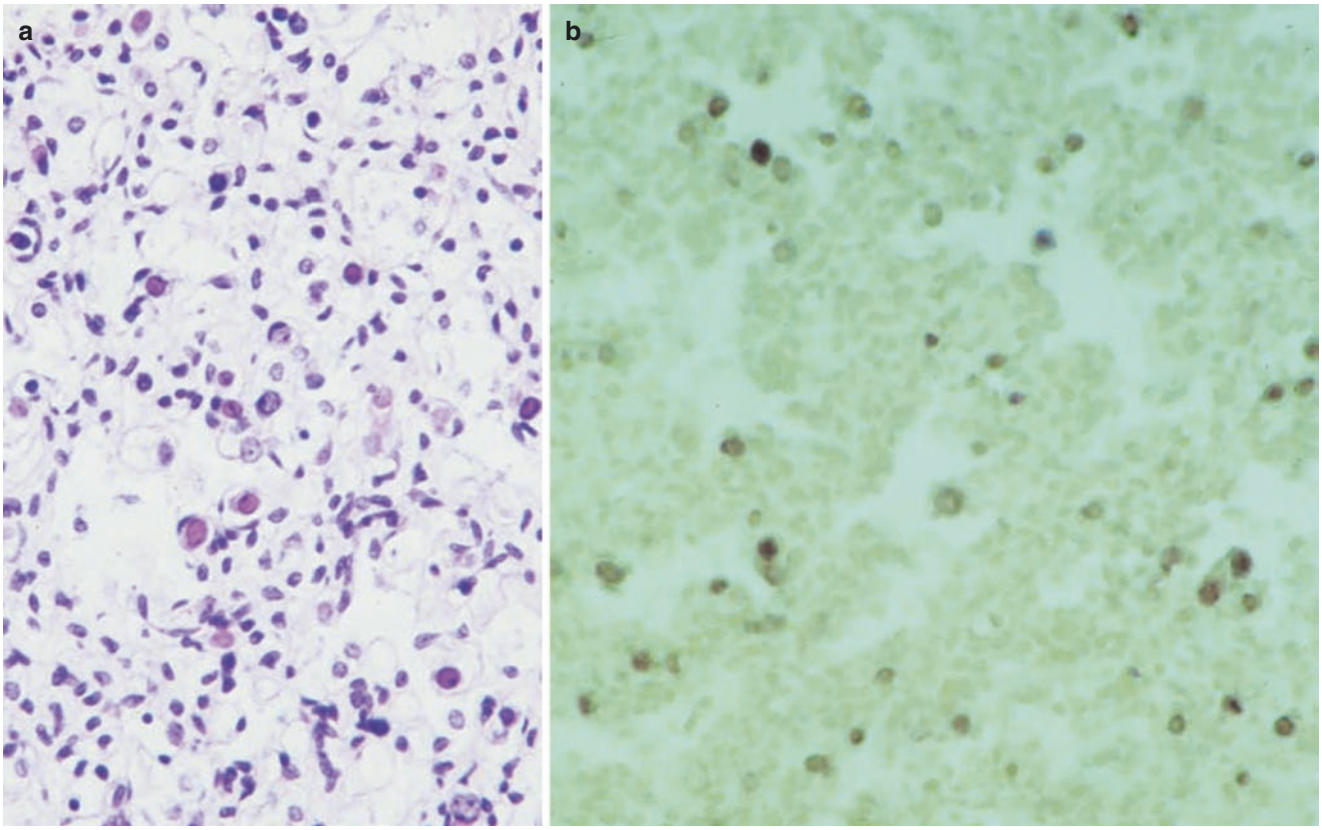

Fig. 13.21 Parvovirus infection. (**a**) Intranuclear inclusions in pulmonary capillary endothelial cells. (**b**) In situ hybridization demonstrates a large number of infected cells

13.7.3 Placenta

The placenta and umbilical cord can show changes associated with fetal hydrops. The placenta is often extremely thick and heavy, may weigh more than 1000 g, and appear pale with friable parenchyma. The changes, however, can be focal or absent. Severity of fetal and placental hydrops does not always correlate well. For example, in congenital nephrotic syndrome, the placental edema can be prominent, even if the fetus is mildly affected.

Twin placentae with TTTS often show pale, friable and thicker parenchyma in the donor's territory, and thinner, congested parenchyma related to the recipient. Vascular communications between the two circulations can be demonstrated by injection studies. The clinically significant vascular shunting takes place within the deep placental parenchyma (Fig. 13.22).

On histological examination, the placenta shows villous edema and relative villous immaturity and nucleated red blood cells in the villous vessels. Mineralisation of the trophoblastic basement membranes is a nonspecific finding. There are other histological features, which are related to the underlying pathology leading to hydrops. Chronic villitis and viral inclusions are seen in congenital infections. Chorangiomas, especially, large ones can cause fetal hydrops (Fig. 13.23). In congenital nephrotic syndrome, the villi may be uniformly edematous and Hofbauer cells are readily seen. In immune hydrops, severity of placental changes usually parallel that of fetal hydrops. However, changes can be patchy in distribution with many villi that are of normal size. Careful examination of the non-hydropic villi shows plugging of villous capillaries by clumps of erythropoietic cells (Fig. 13.24). Similar capillary plugging by tumor cells is seen (Fig. 13.25) in placentas of fetuses with neuroblastoma. Cytoplasmic vacuolation of trophoblast cells is seen in some metabolic storage disease (Fig. 13.26).

It is evident that careful consideration must be given to all pathological findings in the examination of the hydropic fetus. Assessment of histological changes may permit observations in respect of the chronology of changes present and contribute to our understanding of the mechanisms of fetal hydrops.

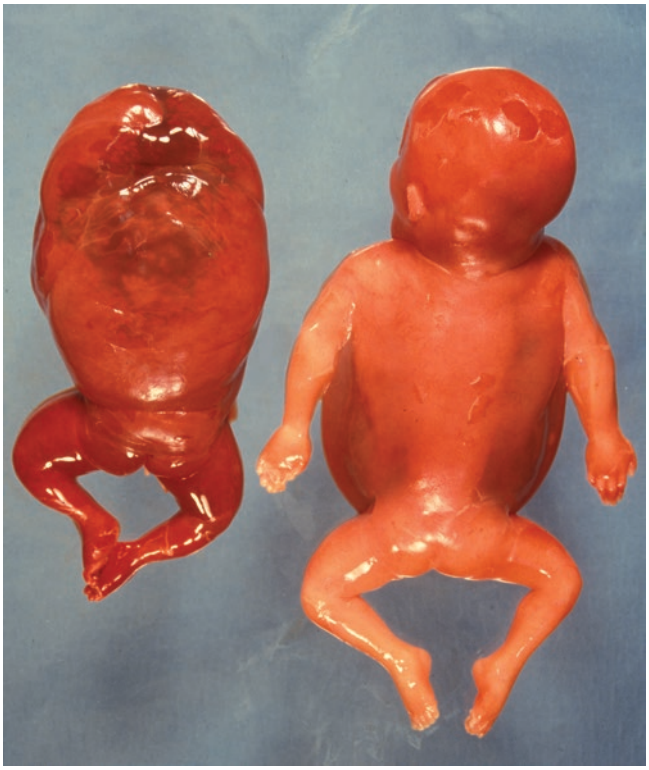

Fig. 13.22 Acardiac twin (left): plethotic. Pump twin (right): anemic and hydropic

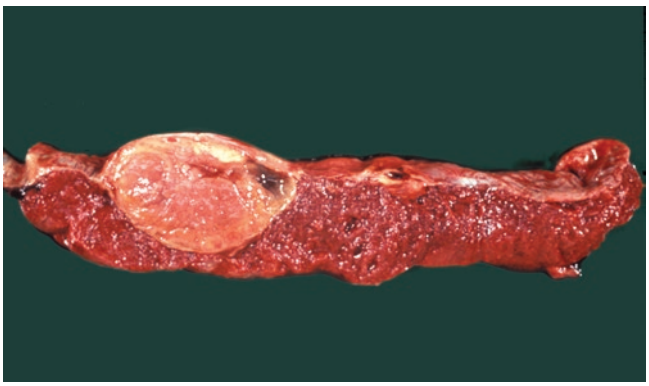

Fig. 13.23 Large angioma in the placenta from a pregnancy complicated by third trimester fetal hydrops and polyhydramnios

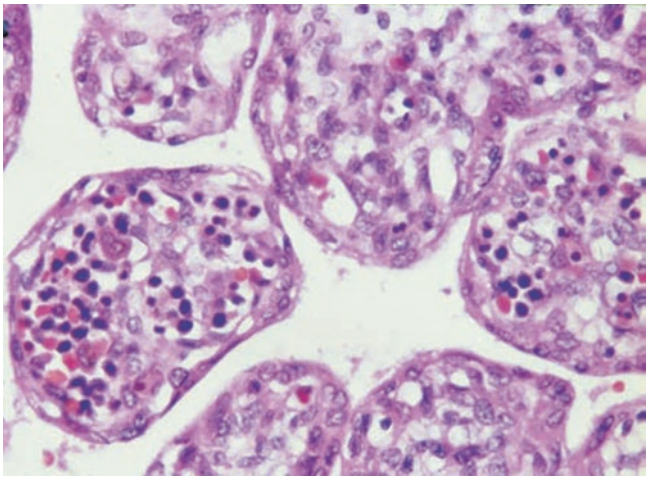

Fig. 13.24 Immune hydrops (Rhesus). Placenta with non-uniform hydropic changes. Capillaries of non-hydropic villi plugged with erythropoietic cells

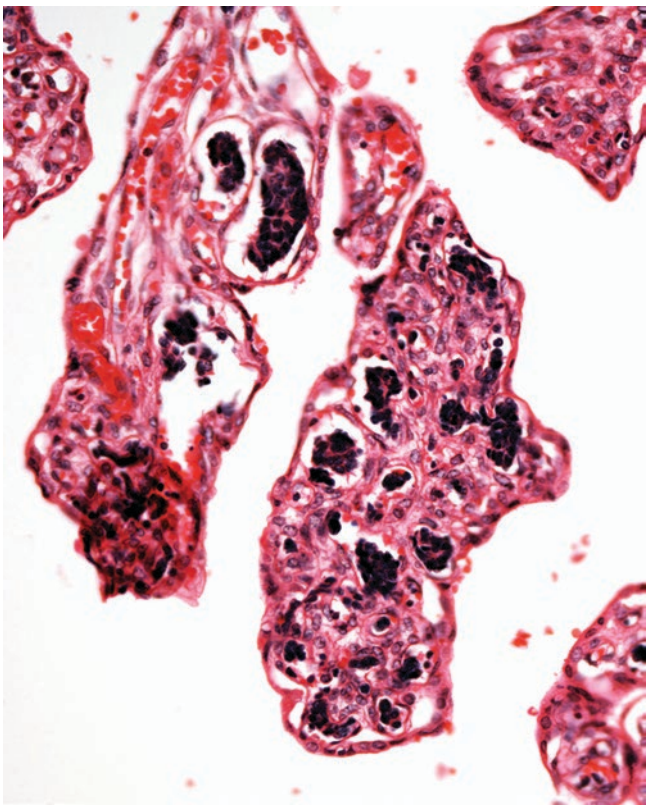

Fig. 13.25 Hydropic fetus with neuroblastoma. Tumor emboli within villous capillaries in the placenta

13.8 Prenatal Therapy for Fetal Hydrops

A number of different types of prenatal interventions for the treatment or prevention of fetal hydrops have been tried, with some success to date. Some of these prenatal therapies are summarized in Table 13.7.

In cases of fetal tachycardia, anti-arrhythmic drugs, such as digoxin or beta-blockers, can be administered to the mother or directly to the fetus to counteract the often poor or unpredictable placental drug transfer that may occur in the hydropic feto-placental unit [242, 243]. Current modes of transplacental administration of antiarrhythmic agents include intraumbilical, intraamniotic, intraperitoneal, intramuscular and intracardiac [244–246]. Fetal cardiac pacing is an effective method to restore sinus rhythm in drug-resistant or hemodynamically unstable cases. Fetal bradycardia is

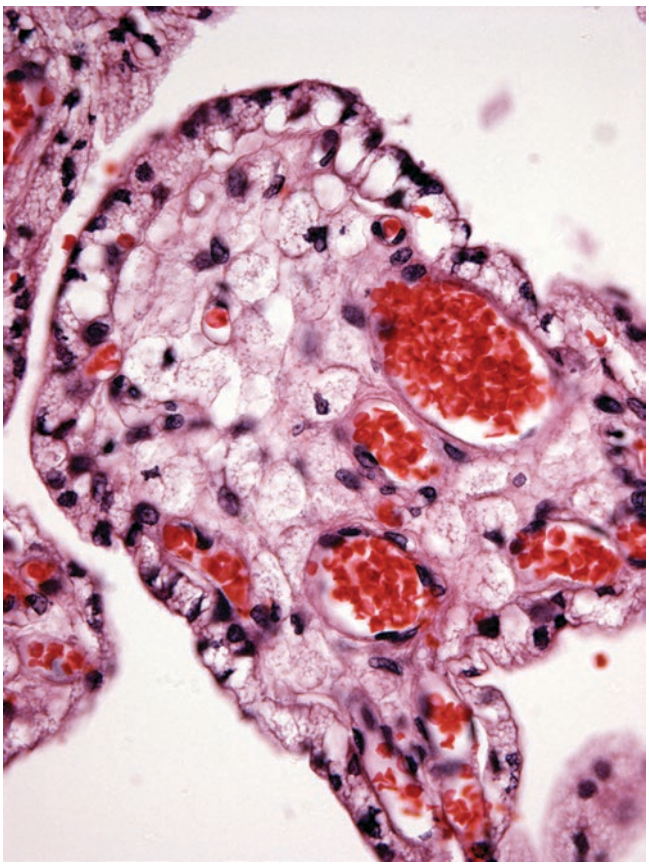

Fig. 13.26 Metabolic storage disease (sialidosis). Prominent, vacuolated trophoblast and Hofbauer cells

Table 13.7 Prenatal therapies for fetal hydrops

Therapy	Etiology
Intrauterine transfusion for anemia	Fetal-maternal hemorrhage Fetal hemolysis Parvovirus B19 infection
Fetal needle drainage of effusion Thoraco-amniotic shunting Pleurodesis, sclerotherapy	Pleural effusion, chylothorax Thoracic cystic lesions e.g. sequestration, CPAM Ascites
Anti-arrhythmic drugs (maternal, transplacental or direct fetal medications) Fetal pacing	Fetal tachyarrhythmia Fetal bradycardia, including atrioventricular block
In utero cardiac catheterisation	Congenital heart disease
Open fetal surgery	Sacrococcygeal teratoma, CPAM
US guided fetoscope Ex utero intrapartum treatment (EXIT)	CHAOS
Laser ablation of placental anastomosis, selective termination	TTTS
Reducing vascular supply	Coiling, embolization, sclerotherapy, laser, radio frequency ablation
Antithyroid drugs	Fetal thyrotoxicosis

CHAOS congenital high-airway obstruction syndrome; *CPAM* congenital pulmonary airway malformation; *TTTS* twin to twin transfusion syndrome

commonly caused by fetal atrioventricular block, for which transplacental administration of β-stimulants, such as ritodrine, terbutaline, and salbutamol have been reported to be effective. Transplacental administration of steroids, such as dexamethasone and betamethasone, are effective for fetal atrioventricular block caused by positive maternal autoantibodies, and for the treatment of myocarditis [247].

One of the ultrasound guided treatment modalities is *in utero* cardiac catheterization combined with detailed fetal Doppler ultrasound assessment. Miniaturization of balloon catheters has the potential for salvage of conditions such as pulmonary stenosis and biventricular outflow tract obstruction and may prevent the development of hydrops in these conditions as well as contribute to the treatment of fetal aortic stenosis—thought to be a precursor lesion in the hypoplastic left heart syndrome [248]. Early stage intervention allows the plastic cardiovascular system to return to a more normal status, and reduces the negative consequences to morbidity and mortality.

Thoraco-amniotic drainage of pleural effusions/chylothorax or large cysts of congenital pulmonary airway malformation [249, 250] to encourage lung growth is now relatively frequently undertaken, with survival (57%) in one study limited mainly by premature labor [251]. Successful outcomes have also been achieved with a similar approach in pulmonary sequestration [252, 253]. Likewise, drainage of ascites or the urinary bladder in order to reduce intra-abdominal pressure may be beneficial. Sclerotherapy with OK-432 was of benefit in an enlarging cystic hygroma [254].

Open fetal surgeries (eg. pulmonary lobectomy for CCAM) has been successful with a fetal survival rate of about 50–60% [255]. *Ex utero* intrapartum treatment (EXIT) is a surgical procedure for hydropic fetuses with congenital high-airway obstruction (CHAOS) [256, 257].

Open total or partial resection of the tumor has been performed in sacrococcygeal teratomas; alternative techniques are feeding vessel ablative therapy or fetoscopic resection to limit the risks to mother and fetus of midgestation hysterotomy [258]. Fetal blood transfusion and albumin infusion have been used in various circumstances such as Parvovirus B19 infection [259, 260], ascitic/hydropic RhD alloimmunization [261], and idiopathic hydrops [262].

Radiofrequency ablation of the blood flow to an acardiac twin is an effective therapy for the hydropic pump twin [263].

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