Fetal Hydrops

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Abstract

Hydrops fetalis, meaning "edema of the fetus," is a clinicopathological term describing an end-stage status of fetal fluid imbalance, and the diagnostic criteria include generalized skin edema with one or more serous cavity effusions. The underlying causes include various maternal, fetal, and placental conditions. Even if the underlying forces to edema formation are the same as has been described in adults (Starling forces), the unique features of fetal physiology, including characteristics of fetal microcirculation and immaturity of the developing organs, predispose to fetal edema formation. This chapter aims to provide some insight into the underlying pathophysiological mechanisms and should help to rationalize and categories the myriad conditions that may give rise to fetal hydrops. A better understanding of the various processes at work in the generation of hydrops provides more information for parental counseling and for more targeted antepartum/perinatal treatments. The importance of postmortem examination, including ancillary investigations, cannot be emphasized enough. Recent publications highlight the usefulness of immunohistochemical assessment of lymphatic vessels in idiopathic cases. It has been also shown that, when postmortem examinations are completed along with clinical assessments, the underlying causes can be found in very high percentage of the cases (>90 %).

Keywords

Fetal hydrops • Hydrops fetalis • Edema • Immune fetal hydrops • Fetal hemolytic anemia Nonimmune fetal hydrops • Chromosomal abnormality • Fetal fluid dynamics • Fluid balance • Autopsy • Placenta • Infection • Developmental abnormality • Immune • Nonimmune • In utero therapy

Hydrops fetalis, meaning "edema of the fetus," is a clinicopathological term describing an end-stage status of fetal fluid imbalance, and the diagnostic criteria include generalized skin edema with one or more serous cavity effusions. The underlying causes include various maternal, fetal, and placental conditions [1].

Even if the underlying forces to edema formation are the same as has been described in adults (Starling forces), the unique features of fetal physiology, including characteristics of fetal microcirculation and immaturity of the developing organs, predispose to fetal edema formation. This chapter aims to provide some insight into the underlying pathophysiological mechanisms and should help to rationalize and categories the myriad conditions that may give rise to fetal hydrops. A better understanding of the various processes at work in the generation of hydrops provides more information

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for parental counseling and for more targeted antepartum/perinatal treatments.

The importance of postmortem examination, including ancillary investigations, cannot be emphasized enough. Recent publications [2, 3] highlight the usefulness of immunohistochemical assessment of lymphatic vessels in idiopathic cases. It has been also shown that, when postmortem examinations are completed along with clinical assessments, the underlying causes can be found in very high percentage of the cases (>90 %) [4].

Global Patterns and Incidence

Traditionally, fetal hydrops has been divided broadly into immune and nonimmune subcategories. The prototype of the immunologic group is fetal hemolytic anemia due to Rh 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. The nonimmune etiologies now constitute approximately 80 % of cases.

Fetal hydrops can be detected throughout the pregnancy. In the first half of the pregnancy, chromosomal abnormality is the most frequently implicated cause [5]. However, 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 [5–9]. A significant portion of the cases are still of unknown cause in most of the studies published.

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 [10].

Hydrops fetalis (including immune and nonimmune cases) is estimated to affect around 1 in 3000 pregnancies [5, 11]. In a study from the UK, 87 hydrops cases (immune and nonimmune) were detected among 13,980 pregnancies giving the rate of 6.2 in 1000 pregnancies [5], 4 out of which were related to red cell isoimmunization (4.6 %) and 83 cases (95.4 %) were nonimmune-related hydrops.

The incidence of live born immune and nonimmune hydrops in Trainor's study was 1.34 per 1000 live births, and 80 % of these cases were nonimmune hydrops [12]. Takci had found a slightly higher rate of 3.8 per 1000 live births with an incidence of nonimmune hydrops in 2 per 1000 live births [13].

Morbidity and Mortality

The mortality rate in fetal hydrops is generally considered to be high (Table 12.1) [5, 10, 14–17].

Early detection of hydrops with chromosomal anomalies (either lethal/non-lethal structural anomalies) is followed by termination of the pregnancy in approximately 23.8 % of the cases, with rates varying between 7.5 % [10] and 72.5 % [14]. The proportion of the cases resulting in spontaneous intrauterine death is very similar to this (24.9 %) with a range of 3.4 % [17] and up to 55.5 % [15]. Fukushima et al. found

Table 12.1 Mortality of nonimmune fetal hydrops

	Termination of pregnancy (lethal and nonlethal causes)	Intrauterine death	Live birth	Neonatal death
Heinonen et al. [14][a]	72.5 % (42/58)	15.5 % (9/58)	12 % (7/58)	28.57 % (2/7)
Sohan et al. [5][b]	37.3 % (31/83)	19.2 % (16/83)	43.3 % (36/83)	30.55 % (11/36)
Fukushima et al. [15][c]	10.8 % (26/240)	<22 weeks 28.4 % (35/240)	60.4 % (145/240)	37.2 % (54/145)
		>22 weeks 27.1 % (34/240)		
Santo et al. [16]	21.2 % (15/71)	17 % (12/71)	62 % (44/71)	22.7 % (10/44)
Moreno et al. [10]	7.5 % (4/53)	30 % (16/53)	43.4 % (23/53)	43.5 % (10/23)
Ng et al. [17]	31 % (9/29)	3.4 % (1/29)	65.5 % (19/29)	57.9 % (11/19)
Overall outcome	23.8 % (127/534)	24.9 % (133/534)	51.3 % (274/534)	18.3 % (98/534) overall 35.76 % (98/274) live births

Modified from the studies listed [5, 10, 14–17]

[a]In the study, there were 5 viable newborns and 2 perinatal deaths but no further specification of the perinatal deaths, and we counted the two perinatal deaths as neonatal deaths

[b]Study of 87 hydrops cases: 4 of which were rhesus alloimmunization (all 4 cases survived till neonatal period) and been excluded from our table

[c]Study analyzed 240 nonimmune hydrops cases, 214 out of which were nonterminated. We included the total number of cases studied in this table

that the numbers of spontaneous fetal losses before and after 22 weeks of gestation were 28.4 and 27.1 % [15]. Currently, over 50 % of the antenatally diagnosed hydrops cases are born alive (51.3 %). The best survival rate was described in Ng et al.'s study (65.5 %) from Japan, and the worst was reported in Heinonen et al.'s study (12 %) from Finland. However, in the latter study, the author reported two perinatal deaths and five viable newborns, and it was not clear whether the two perinatal deaths represented neonatal or intrauterine deaths. Approximately one-third (35.3 %) of live born died in the neonatal period. The rate of neonatal deaths ranges between 22.7 % [16] and 57.9 % [17].

It was found that the likelihood of neonatal death was related to fetal maturity, condition at birth (Apgar scores), and respiratory support requirements [13, 18]. The underlying cause was also considered to be an important factor in neonatal mortality. The highest mortality rates were seen among neonates with congenital anomalies (57.7 %) and the lowest among neonates with congenital chylothorax (5.9 %) [18]. Idiopathic cases are frequent in the survivors [12, 14, 17].

Fukushima examined survival in nonimmune fetal hydrops, which was found to be increased when the diagnosis of hydrops was made at later gestational age. Survival rates were 18.8 %, 33.3 %, 44.6 %, and 66.7 %, corresponding to diagnoses before 22 weeks', between 23 and 25 weeks', between 26 and 29 weeks', and over 30 weeks' gestation, respectively [15].

Fukushima et al. also followed 56 ex-hydropic infants for a longer period and found that 32.8 % of the children had some evidence of neurological impairment, 15.5 % had suspected neurological abnormalities, but 51.7 % were normally developed. Interestingly, they found that even if the survival rate increases with later detection of the hydrops (as previously mentioned), intact neurological development had an inverse correlation with the gestational age. Normal neurological development was found in 71.5 %, 60.0 %, 50.0 %, and 43.3 % of the surviving hydrops cases (at 1-year follow-up) when hydrops fetalis was detected before 22 weeks, between 22 and 25 weeks, between 26 and 29 weeks, and over 30 weeks of gestation. They also found that, in 57.9 % of the cases, there were other factors contributing to the neurological outcome, including chromosomal abnormalities, low birth weight, and traumatic brain injury. Therefore, long-term neurological developmental outcome is partly dependent on the underlying cause of hydrops [15].

Haverkamp et al. followed 28 nonimmune hydrops survivors for neurological, cognitive, and motor functions. They found that the survival is related to the severity of intrauterine hydrops (i.e., the less severe, the better the survival) and confirmed that the neurological prognosis is more related to the underlying disease. In that study, 85.7 % of the patients had normal neurological status, 7.2 % had minor dysfunctions, and 7.2 % had spastic cerebral paresis [19].

Clinical Presentation

Fetal hydrops may present at any gestation from the first trimester to term. It may also be unexpectedly recognized at birth on occasion. Owing to improvements in diagnostic techniques, particularly fetal ultrasound, detection now more often occurs in early gestation. Likewise, categorization of any underlying structural abnormalities has become more precise, providing a better correlation with risk and outcome and allowing an improvement in parental counselling.

In the first trimester, hydrops is usually detected at an asymptomatic stage during routine ultrasound scanning or in spontaneous miscarriages. These early diagnosed cases are usually syndromic, many with identifiable chromosomal aberrations. Prominent translucencies, the so-called fetal 'space-suit' hydrops, in the first trimester indicate an even higher risk of chromosomal abnormality than isolated nuchal translucency [20]. These early pregnancies usually result in spontaneous miscarriage, intrauterine fetal death, or elective termination [5, 21]. In the second half of the pregnancy (especially in the third trimester), hydrops is more often due to other diseases, principally in relation to cardiac malformations.

Clinical presentation includes generalized subcutaneous or nuchal edema as well as serous cavity effusions (pleural, pericardial, and peritoneal). These fetuses are large for gestational age and the placenta is enlarged, thickened, and edematous. Polyhydramnios and even maternal edema (mirror syndrome) may be present. Altered fetal hemodynamics, fetal tachycardia, decreased fetal movements, abnormal serum screening, and antepartum hemorrhage are also featured in some of the cases.

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 [22]. Unexplained cases could also benefit from referral to a medical genetics service.

Fetal Fluid Dynamics

The fetus has very high total body water content. In the embryo, 90–95 % of the body weight is fluid, which gradually decreases to about 80 % by 8 months gestation and to around 75 % at term [21].

As in adults, fetal edema is caused by accelerated water flow through the capillary walls into the extravascular spaces and/or impaired reabsorption of fluid from the interstitium back to the circulation. Transcapillary 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 [23]. The fetal interstitial space is more compliant, and the interstitium can accommodate more fluid without significant increase in the hydrostatic pressure [23, 24]. As the protein lost from the vascular space into the interstitium needs to be returned into the circulation via lymphatic vessels, the lymph flow is four- to fivefold higher than in adults [25]. 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 [26]. The placenta also has an important role in fetal fluid balance [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].

Maintenance of fluid homeostasis and critical organ perfusion (blood redistribution to the brain, adrenals, and heart) is under hormonal, renal, and behavioral (i.e., swallowing) control [29]. The gestational age and, therefore, the development status of these reflexes, as well as hormonal mechanisms, have significant impacts on fluid homeostasis. The renal angiotensin system (angiotensin II) has a central role in blood pressure regulation and diuresis. Other hormones are the natriuretic peptides (ANP, BNP), which respond to volume load and hyperosmolality and are effective vasoconstrictors [30]. Aldosterone has a limited role in utero due to immaturity of this regulatory mechanism. AVP (vasopressin) decreases water reabsorption in the collecting duct and reduces urine concentration. However, this has a lesser effect in the immature kidney [29].

Amniotic Fluid

The amniotic fluid surrounds the fetus, provides mechanical protection and space for normal growth and development, and contains nutrients, growth factors, and antimicrobial peptides. Its volume, production, and chemical composition alter throughout a pregnancy. In early gestation, the liquor is filtered from maternal plasma across the fetal membranes, based on hydrostatic and osmotic forces. As the placental vasculature develops, the maternal fluid mainly passes across the placenta to the fetus and thence from the fetus to the amniotic cavity.

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 [31]. The diffusion is bidirectional and crosses the nonkeratinized skin and amniotic epithelium-lined surface (i.e., umbilical cord and chorionic plate) [32]. 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 not linear any longer. There are various pathways of maternofetal fluid exchange. The two main sources of amniotic fluid are fetal urine and lung fluid secretions. The lung fluid expands and promotes airway development, and the excess fluid flows out of the trachea and either is swallowed or enters the amniotic cavity [33]. The intramembranous pathway is a flow across the amniotic membranes but varies in amount [34]. The transmembrane pathway is a flow across the fetal membranes into the uterine (maternal) circulation [35, 36].

Additional pathways have been suggested recently. The presence of transcellular vesicular transport of the amniotic fluid into the intramembranous microvasculature was suggested [34]. Vascular endothelial growth factor (VEGF) not only regulates growth of the blood vessels in the fetal surface of the placenta and in the membranes but also increases vascular permeability enhancing intramembranous amniotic fluid absorption [37]. Aquaporin water channels are the other newly described pathway [27, 38, 39].

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 [26].

Causes and Mechanisms of Fetal Hydrops

The list of diseases associated with hydrops fetalis is long and ever-expanding with new entities (Table 12.2) [11, 40–212]. According to a recent systematic review, Bellini et al. [1] have identified 51 case series relating to nonimmune hydrops, describing 5437 cases in total and classified the cases into diagnostic categories (Table 12.3) [1, 9, 10, 13, 15–17]. We also include further studies in the summary table that have been published since 2008.

The most frequent categories of nonimmune hydrops include idiopathic (11.5–33.6 %), cardiovascular (7.5–27 %), chromosomal (2.6–28.3 %), infectious (2.9–18.3 %), hematological (1.9–42.3 %), and genetic/metabolic (1.1–14 %). Not surprisingly, the study from Thailand [9] showed more hematological causes, as thalassemia is common in that part of the world.

Table 12.2 Abnormalities associated with fetal hydrops [11, 40–212]

Cardiac abnormalities	
Structural abnormalities	*Arrhythmias*
Complex anomaly with ambiguous cardiac situs [40, 41]	Supraventricular tachycardia [40, 55]
Tetralogy of Fallot [40]	Paroxysmal atrial tachycardia [43, 55]
Hypoplastic left heart syndrome [11, 42]	Junctional ectopic tachycardia [56]
Transposition of great arteries [41, 42]	Complete heart block [42, 51, 57, 58]
Truncus arteriosus [42, 43]	Complete heart block and maternal connective tissue disease [59, 60]
Atrioventricular canal defect [40, 44]	Bradycardia [43]
Double-outlet right ventricle [45, 46]	Bundle branch block [61]
Single ventricle [42]	Arrhythmia and conduction system anomaly [62, 63]
Pulmonary valve atresia [44, 47]	Tachyarrhythmia – virus induced [64]
Absent pulmonary valve + EFE [40, 48]	Wolff–Parkinson–White syndrome [65]
Aortic valve stenosis/atresia [44, 48, 49]	Long QT syndrome [66]
Tricuspid valve atresia [41, 42]	*Other cardiac pathology*
Tricuspid valve atresia and ectopia cordis [44]	Myocarditis [41, 67]
Ebstein anomaly [44, 48]	Myocardial infarction [coronary artery embolus] [40]
Mitral atresia + EFE [50]	Cardiomyopathy [42, 44]
Atrial septal defect [42]	Noncompaction cardiomyopathy [68]
Large ventricular septal defect [42, 51]	Premature closure of foramen ovale [70–72]
Noonan syndrome [52]	Premature closure of ductus arteriosus [72–75]
Arcadia [twin pregnancy] [40, 53]	Endocardial fibroelastosis ± hepatitis [41, 76]
Aorto-left ventricular tunnel [54]	Right atrial aneurysm [77]
	Cardiac diverticulum [78]
Vascular abnormalities	**Chromosomal/genetic anomalies**
Hemangioma	45XO [40, 95]
Fetus [41, 79]	90XX [96]
Fetus multiple [80]	Trisomy 21 [42, 49]
Atrial angioma [81]	Trisomy 18 [41, 97]
Coronary artery embolus [40]	Trisomy 13 [95, 98]
Calcific arteriopathy [41, 82]	Trisomy 15 [99]
Descending thoracic aortic aneurysm [83]	Triploidy [11]
Abdominal aortic coarctation [84]	Trisomy 10 mosaicism [100]
Meningeal angiomatosis [53]	Pallister–Killian syndrome [tetrasomy 12p] [101]
Megalencephaly–capillary malformation syndrome [85]	Partial trisomy 19q [102]
Vena caval thrombus [86]	Mosaic tetrasomy 9p [103]
Superior caval vein obstruction [87]	Unbalanced translocation t[3;7] [104]
Agenesis of ductus venosus [88–90]	Unbalanced translocation t[8;11] [105]
Agenesis of portal or hepatic veins [91]	1p36 deletion [106]
Abnormal course of inferior vena cava [91]	6p deletion [107]
Pulmonary lymphangiectasia [11]	Interstitial deletion 10q22.3-q24.1 [108]
Diffuse lymphangiectasia [92, 93]	22p11 microdeletion [109]
Cystic hygroma [41, 51]	Distal 5q duplication [110]
Familial pulmonary lymphatic hypoplasia [94]	Noonan-like syndrome [c.4A>G missense changes in *SHOC2*] [111]
	Mutations in lymphangiogenic genes [*VEGFR3* and *FOXC2*] [112]
	Hereditary lymphedema syndrome with *FOXC2* mutation [113]
Metabolic diseases	**Anemia and other hematological diseases**
Infantile Gaucher [43, 67]	Rhesus incompatibility [128]
Mucopolysaccharidosis [95, 114, 115]	ABO incompatibility [59, 129]
Sialidosis [116, 117]	Kell incompatibility [130, 131]
Galactosialidosis [118]	Alpha thalassemia [42, 132]
Niemann–Pick [119]	Hemoglobin Bart's [133, 134]
GM_1, gangliosidosis [51]	Hemoglobin Bart's + H [135]
Hypoalbuminemia [120]	Hemophilia A [95]
Long-chain acyl-coenzyme A dehydrogenase deficiency (LCHAD) [121]	Pyruvate kinase deficiency [136, 137]
Fatal perinatal neuromuscular glycogenosis (type IVA) [122]	Glucose-6-phosphate dehydrogenase deficiency [138, 139]
Carnitine deficiency [123]	Diamond–Blackfan syndrome [140, 141]
Neonatal hemochromatosis [124]	Dyserythropoietic anemia [142, 143]
Congenital erythropoietic porphyria (Gunther disease) [125]	Congenital xerocytosis [144]
Congenital disorder of glycosylation type Ia [126]	Transient myeloproliferative disorder in trisomy 21 [145]
Autophagic vacuolar myopathy-like disorder [127]	Familial hemophagocytic lymphohistiocytosis [146, 147]
	Chronic fetomaternal hemorrhage [68, 148]
	Fetomaternal hemorrhage (choriocarcinoma) [149, 150]
	Hemorrhage into fetal organs
	Intracranial with ischemia [51, 151, 152]
	Intracranial with tumor [53]
	Intra-abdominal [153]

(continued)

Table 12.2 (continued)

Congenital infections Parvovirus B19 [154–156] Cytomegalovirus [11, 42] Human herpes virus type I [43] Rubella virus [76] Toxoplasmosis [76, 157] Syphilis [158, 159] Coxsackie virus [160] Myocarditis NOS [41, 67] Adenovirus [64, 161] Candida [162] Enterovirus [163]	**Intrathoracic abnormalities** Pulmonary agenesis [164] Tracheobronchomalacia [165] Adenomatoid malformation [40, 41] Pulmonary sequestration [40, 51] Congenital high airway obstructive syndrome (CHAOS): Laryngeal or tracheal atresia [41, 67] Mainstem bronchial atresia [166] Mesenchymal hamartoma [167] Diaphragmatic hernia [40, 41] Accessory diaphragm [168]
Gastrointestinal and liver abnormalities Esophageal atresia [169] Jejunal atresia [76] Small intestinal volvulus [153] Meconium ileus ± peritonitis [11, 51] Intestinal infarction [42] Intestinal obstruction [95] Hepatitis [11, 41] Hepatic necrosis [11] Cirrhosis [41, 76]	**Urogenital abnormalities** Renal hypoplasia [41, 51] Cystic renal dysplasia [169] Meckel syndrome [53] Fraser syndrome [41, 170] Autosomal recessive kidney disorder [171] Mesoblastic nephroma [79, 172] Bartter syndrome and unilateral ectopic renal cyst [173] Congenital nephrotic syndrome [67, 174] Urethral obstruction Valves [42] Atresia [41] Vaginal atresia, hydrometrocolpos syndrome [11, 49] Cystic malformation of the lower female genital tract [175] Fetal gonadoblastoid testicular dysplasia [176]
Musculoskeletal abnormalities Achondrogenesis I [67] Achondrogenesis II [49, 177] Osteogenesis imperfecta [11, 67] Thanatophoric dysplasia [178] Asphyxiating thoracic dystrophy (Jeune) syndrome [11] Short rib-polydactyly, type I (Saldino–Noonan) syndrome [179] Greenberg dysplasia [180] Ellis–van Creveld syndrome [95] Desbuquois dysplasia type I [181] Congenital cortical hyperostosis (Caffey disease) [182] Neu–Laxova syndrome [42] Multiple pterygium syndrome [42] Popliteal pterygium syndrome [95] Fetal akinesia deformation sequence (Pena–Shokeir, type I phenotype) [42] Myotonic dystrophy [95] Myopathy with muscle spindle excess [183] Amniotic bands [42] *Other fetal anomalies* Hyperthyroidism [202] Incontinentia pigmenti [203] Simpson–Golabi–Behmel syndrome [204] Oral–facial–digital syndrome [171] *Placenta* Hemangioma [41, 205] Chorioangioma [206] Placental mesenchymal dysplasia [207] Abnormal course of umbilical vein [91] Fetal entanglement with umbilical cord [41] Umbilical cord torsion [208] *Multiple pregnancy* Acardiac monozygous twin pregnancy [40, 53] Fetofetal hemorrhage (twin transfusion syndrome) [41, 95]	**Central nervous system abnormalities** Hydrocephaly, arthrogryposis [42] Holoprosencephaly [67] CNS destruction, hypomobility [184] *Congenital tumors* Rhabdomyoma and tuberous sclerosis [40, 41, 185] Cardiac rhabdomyoma [41, 185] Cardiac teratoma [95, 186] Atrial angioma [187] Congenital peribronchial myofibroblastic tumor [188] Neuroblastoma [49, 189] Primitive neuroectodermal tumor [53] Mesoblastic nephroma [172] Nephroblastoma [190] Rhabdoid tumor of the kidney [191, 192] Hepatoblastoma [193] Hepatic mesenchymal hamartoma [194] Glioblastoma multiforme [195] Teratoma Sacrococcygeal [11, 196] Mediastinal [178, 197] Intrapericardial [42, 95, 186] Congenital leukemia, Down syndrome [198, 199] Retroperitoneal kaposiform hemangioendothelioma [200] Cervical fibrosarcoma [201] *Maternal disorders* Rheumatological disorders [60, 209] Antiphospholipid antibody syndrome [210] Diabetes mellitus [211] Maternal anemia with two hydropic pregnancies [97, 169] Choriocarcinoma [212]

Table 12.3 Categories of nonimmune fetal hydrops [1, 9, 10, 13, 15–17]

Study	Idiopathic	Cardiovascular	Chromosomal	Genetic and metabolic	Hematological	Infection	Syndromic	Thoracic, GI and liver	Urogenital	Lymphatic dysplasia[a]	Other
Bellini et al. [1]	17.8 %	21.7 %	13.4 %	1.1 %	10.4 %	6.7 %	4.4 %	6.5 %	2.3 %	5.7 %	10 %
Taweevisit et al. [9]	11.5 %	27 %	2.6 %		42.3 %	6.4 %		9 %			1.3 %
Santo et al. [16]	18.3 %	9.8 %	2.8 %	14 %	7 %	18.3 %		18.3 %		4.2 %	7.3 %
Fukushima et al. [15]	33.6 %	18.7 %			1.9 %	4.2 %		7.9 %		27.6 %	6.1 %
Moreno et al. [10]	13.2 %	7.5 %	28.3 %	5.7 %		7.5 %	18.9 %				
Ng et al. [17]	31 %	17 %		14 %	14 %					10 %	14 %
Takci et al. [13]	29.4 %	11.8 %	2.9 %	8.8 %	8.8 %	2.9 %				23.6 %	11.8 %

GI gastro-intestinal

[a]Also includes hygroma and chylothorax cases

Lymphatic dysplasia has been recognized by some to be more frequent than by other authors. Lymphatic vessels were examined by immunohistochemistry in recent studies by Bellini et al. [2]. They demonstrated the presence of abnormal lymphatic channels in 17/79 (21.5 %) of the idiopathic nonimmune hydrops cases. The authors suggest adding immunohistochemistry for lymphatics to routine autopsy protocols [3].

The underlying pathological mechanism of nonimmune hydrops can be complex. One structural abnormality can cause multiple functional problems, and various causes can share the same mechanism. Most of the classifications are based on etiology (Table 12.2) rather than mechanism. However, knowledge of the underlying mechanisms and how these interact with each other helps to understand the patterns of presentation and how the process could be reversed therapeutically. We have summarized the main underlying mechanisms of each major etiological category (Table 12.4) [145, 213] and related them in diagrammatic form (Fig. 12.1).

Cardiovascular Disease

The fetal heart and circulation are unique. There are connections between the left and right ventricular circulations (the foramen ovale and ductus arteriosus) that provide alternative pathways in the event of obstruction. The fetal myocardium is structurally and functionally immature, is relatively stiff with reduced relaxation, and has limited preload reserve. Therefore, the developing fetal heart can only increase cardiac output by increased heart rate [214].

The right ventricle is dominant antenatally, and it is sensitive to afterload changes, i.e., increased pressures in the cerebral, systemic, and placental vessels. Right ventricular failure reduces diastolic emptying and increases the end-diastolic pressure and volume in the right atrium with increased systemic/central venous pressure leading to increased hydrostatic intravascular pressure at the capillary level [215]. Venous pressure also can be increased by intra-abdominal lesions (e.g., intra-abdominal mass compressing the great veins) and portal hypertension.

The left ventricular failure reduces the left atrial filling from the inferior vena cava via the foramen ovale, resulting in increased intravascular hydrostatic pressure as in right ventricular failure. Williams et al. suggested another possible mechanism of left ventricular failure when fetal hydrops is not associated with increased central venous pressure [216]. They hypothesized that increased pulmonary venous pressure results in lymphatic pulmonary edema, increasing the lung fluid protein content, which is released into the amniotic fluid.

Cardiac failure causes circulatory deficiency resulting in tissue hypoxia. Prolonged blood redistribution to the critical organs causes ischemic injury to the less perfused organs (i.e., the liver and kidney), further exacerbating hydrops [23].

Chromosomal and Genetic Abnormality

The most common chromosomal abnormalities and malformations are likely to contribute to cardiac failure in various ways (e.g., structurally abnormal heart) and impaired lymphatic drainage via lymphatic malformations. Transient abnormal myelopoiesis is associated with Down syndrome [145].

Genetic diseases with known associations to fetal edema include neuromuscular disease, skeletal dysplasia, and inborn errors of metabolism. The latter can cause hydrops by multiple means, including by inducing cardiac failure (i.e., cardiomyopathy), high cardiac output due to increased metabolic demand, increased portal hypertension, reduced protein production, and bone marrow failure.

Nonimmune Fetal Anemia

Reduced circulating mature red blood cells may be due to deficient production, hemolysis, or hemorrhage. The fetus has a higher risk of developing anemia as the life span of erythroid cells is shorter than in adults [217]. 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), thereby increasing extramedullary hematopoiesis; and aplasia of the erythroid precursors, as in parvovirus B19 infection. Increased destruction of the erythroid elements can be secondary to constitutional disease, infection, and vascular lesions (Kasabach–Merritt phenomenon).

Anemia may cause tissue hypoxia (e.g., renal tubular damage, endothelial damage, cardiomyocyte ischemia, reduced liver function) and high-output cardiac failure.

Intrauterine Infection

Fetal hydrops can be a serious manifestation of intrauterine infection. To date, numerous infective organisms have been described as causes of fetal hydrops. Infection causes endothelial cell damage, leading to leaking capillaries, liver cell necrosis (e.g., HSV, syphilis) with severe liver destruction and dysfunction, and myocarditis (e.g., Coxsackie virus, adenovirus) with arrhythmias. Parvovirus B19 is one of the

Table 12.4 Mechanisms of fetal hydrops

Mechanism of hydrops	Diseases
1. Anemia	
Hemolysis (immune)	Immune-mediated anemia, e.g., rhesus incompatibility
Abnormal hematopoiesis	Transient abnormal myelopoiesis, e.g., Down syndrome (146)
Reduced erythrocytes production	Constitutional diseases Infection/red blood cell aplasia, e.g., parvovirus Bone marrow infiltration Bone marrow space reduction, e.g., skeletal dysplasia Liver disease, e.g., inborn error of metabolism
Hemolysis (nonimmune: extrinsic and intrinsic)	Constitutional diseases Vascular lesions Infections
Hemorrhage	Fetomaternal hemorrhage Hemorrhage into fetal organs (ischemia, tumors) Fetofetal hemorrhage (TTTS)
2. Cardiovascular disease (Modified from Ref. [213])	
Abnormally structured heart (altered hemodynamics)	Structural heart abnormality, e.g., cardiac malformation, diverted blood flow via septal defects
Normally structured heart (functional cardiac failure)	(a) Reduced venous return to right atrium/increased venous pressure External compression of the heart, e.g., intrathoracic SOL, pleural effusion, chest wall restrictions, neuromuscular disease Compression on great vessels in the thorax Compression on great vessels in the abdomen, e.g., intra-abdominal SOL Venous occlusion, e.g., thrombus Portal hypertension, e.g., IEM (b) Other Arrhythmia, e.g., maternal SLE High cardiac output due to increased demand or diverted blood flow, e.g., fistula, vascular malformations, anemia, premature closure of FO/DA, metabolic increase in tumors, and IEM Low cardiac output: reduced blood return to heart, reduced blood volume (e.g., hemorrhage), bradycardia, obstructed outflow Increased left ventricular failure may cause lymphatic edema
Normally structured heart (primary myocyte abnormality leading to functional cardiac failure)	Reduced compliance, e.g., CMP Cardiomyocyte dysfunction, e.g., myocarditis, infection, ischemia, IEM, tumor, CMP Arrhythmia
Vascular disease, including vascular malformations	High cardiac output, e.g., shunting through vascular malformation, tumors, teratomata Hemolysis/anemia Local space-occupying lesions leading to local compression Lymphatic dysplasia, e.g., aneuploidy Congenital vascular malformations, e.g., agenesis of ductus venosus Primary vascular disease, e.g., calcific arteriopathy, aneurysm
Endothelial damage	Hypoxia Infection Inflammation
3. Chromosomal anomalies	
Impaired lymphatic drainage	Lymphatic malformation, e.g., Turner syndrome
Cardiac failure	Cardiac malformation, e.g., Down, Turner, and Noonan syndrome
Abnormal hematopoiesis	Transient abnormal myelopoiesis, e.g., Down syndrome
4. GI and genitourinary rare causes	
Reduced swallowing	Congenital malformations, e.g., esophageal atresia Neuromuscular disease
Reduced protein production	Liver dysfunction, e.g., liver destruction in infection, ischemia, IEM Reduced nutrient supply from the placenta
Renal protein loss	Congenital nephrotic syndrome
Excess urine production	Renal tubular damage, e.g., ischemic damage, renal vein thrombosis

(continued)

Table 12.4 (continued)

Mechanism of hydrops	Diseases
Increased intravascular hydrostatic pressure/reduced venous return to heart	Compression on great vessels, e.g., cystic kidneys, enlarged bladder Increased intra-abdominal pressure, e.g., small intestinal volvulus, intestinal obstruction, tumors Portal hypertension, e.g., IEM
5. Infection	
Increased capillary permeability	Damage to endothelial cells
Reduced protein production	Liver cell destruction, e.g., HSV, syphilis
Cardiac failure	Myocarditis, e.g., Coxsackie virus, adenovirus
Anemia	Red blood cell aplasia, e.g., parvovirus
6. Inherited genetic disease	
Cardiac failure	Cardiomyopathy, e.g., IEM Increased metabolic demand in IEM leads to high cardiac output failure
Hypoproteinemia	Hepatomegaly and reduced liver function, e.g., IEM
Anemia	Constitutional disease Bone marrow infiltration
Reduced venous return	Hepatomegaly with compression of the sinusoids leading to portal hypertension, e.g., IEM
Reduced fetal movements	Neuromuscular disease with skeletal muscle hypotonia, reduced swallowing, e.g., myotonic dystrophy
7. Placenta	
Reduced venous return to the heart	Umbilical vein compression, e.g., intra-abdominal mass, hypercoiled cord
Tissue hypoxia	Reduced oxygenation of fetal blood
	Polycythemia, e.g., TTTS
Anemia	Chorangioma
Cardiac failure	High cardiac outflow, e.g., TTTS
Volume overload	Fluid shift into fetal circulation via placenta
8. Maternal disorder	
Arrhythmia	Fetal arrhythmia, e.g., maternal SLE
Anemia	Fetal anemia

DA ductus arteriosus, *FO* foramen ovale, *IEM* inborn error of metabolism, *SLE* systemic lupus erythematosus, *SOL* space-occupying lesion, *TTTS* twin to twin transfusion syndrome

most common associated infections with hydrops. It infects erythroid precursors and fetal myocardium. The virus has direct toxic effect and induces apoptosis (red blood cell aplasia) [217].

Placenta, Multiple Pregnancies, and Maternal Disease

The placenta also plays an important role in maternofetal fluid balance. Intrinsic problems with the placental circulation contribute to fluid accumulation in the fetal compartments. Reduced blood return from the placenta (e.g., owing to umbilical cord lesions or intra-abdominal masses obstructing the umbilical vessels) not only influences cardiac function but reduces the oxygen and nutrient supply to the fetus. Fetal anemia can be caused by fetomaternal hemorrhage and hemorrhage into chorangiomas. Cardiac failure can be caused by increased resistance in the placental bed and by high cardiac output in twin to twin transfusion syndromes. There are many maternal disease states that are associated with fetal arrhythmia, anemia, and uteroplacental insufficiency.

Other

Thoracic, gastrointestinal, and urogenital abnormalities are well recognized but rare associations with hydrops. The main mechanism is due to compression of the great vessels, thereby increasing the hydrostatic pressure at capillary level or reducing the venous return to the heart. Intrathoracic lesions can cause direct compression to the heart, to the great vessels, or to the esophagus (blocking swallowing of the amniotic fluid). Reduced swallowing either due to neuromuscular disease or atresia reduces amniotic fluid reabsorption, leading to polyhydramnios.

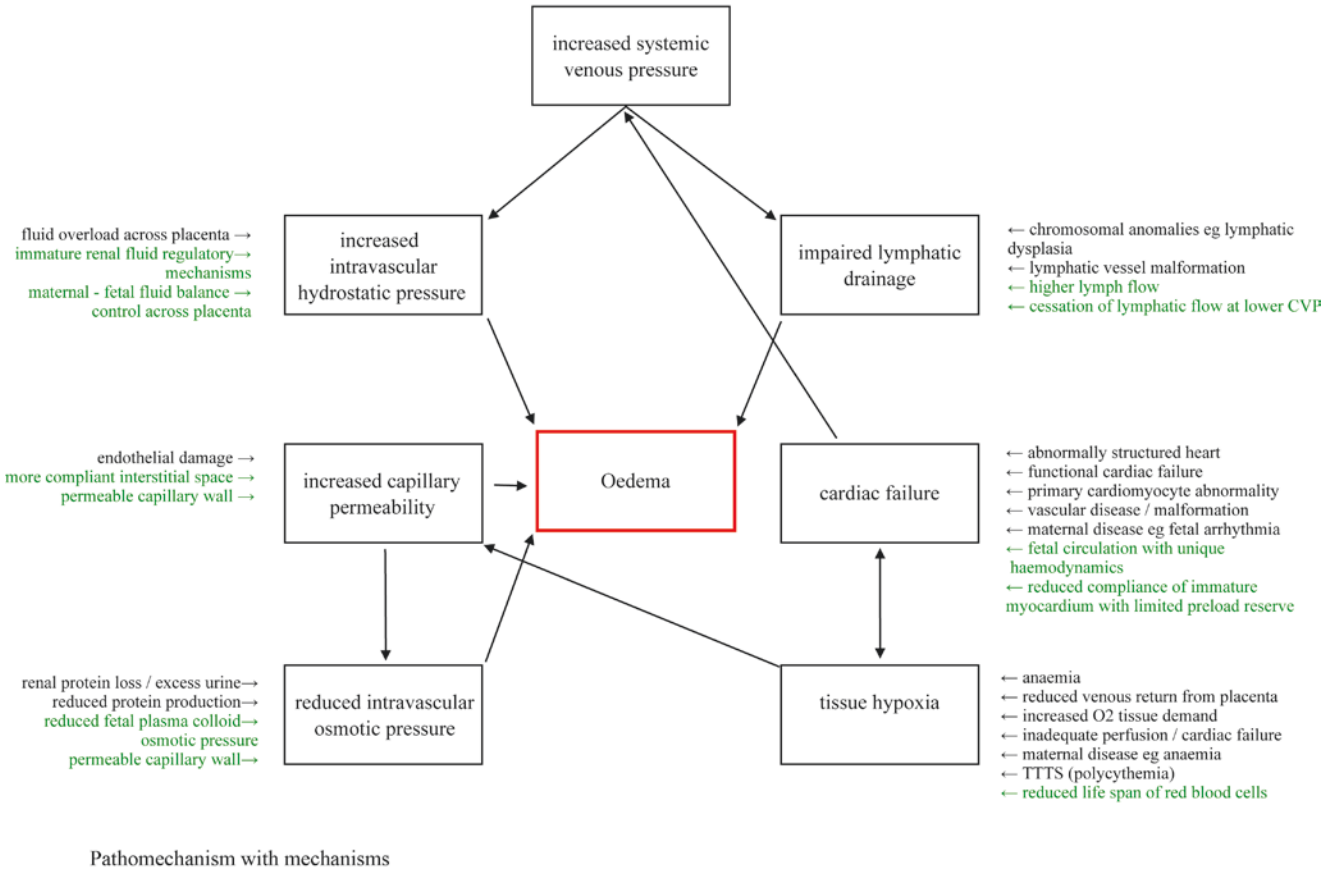

Fig. 12.1 Mechanisms of fetal edema with contributory fetal physiological factors (in *green*)

Investigation of Fetal Hydrops

The aims of investigations following the discovery of fetal hydrops are to ascertain the underlying cause or association and to document the severity of fetal edema, the presence or absence of effusions in body cavities, the degree of polyhydramnios, and the extent of placental involvement. This is to facilitate rational decision making with regard to patient management, and estimates of risk of recurrence can be given (Tables 12.5 and 12.6) [42, 218, 219].

The combination of antenatal and postnatal investigations with postmortem examination is the best combination to reach final diagnosis and to refine the underlying mechanisms. When prenatal, postnatal, and postmortem examinations were completed, the cause was identified in over 90 % of the cases [4, 14].

Pathological Findings

Frequency of hydrops cases in autopsy practice varies. In a study from Thailand, 16 % of stillborn fetuses were hydrops fetalis, and the most common cause of hydrops was anemia [9]. In two other autopsy studies from Rodriguez, frequency of hydrops was 6.07 % in stillbirth cases and 7.45 % in neonatal death cases [220]. The cardiovascular disease was the most common cause (50 %) in live born deaths [211, 220], but it was only 14 % in stillbirth cases. In stillbirths, congenital infection (34 %) was the most frequent cause [4].

External

The affected fetus is usually preterm and pale. 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 (Figs. 12.2, and 12.3b). A disproportionate amount of postnuchal fluid accumulation is usually seen in monosomy X (Fig. 12.3), although it is not specific for this condition and may occur with other chromosome abnormalities or with normal karyotype. The ascites causes abdominal distension (Fig. 12.4a). However, this may well be secondary to hepatomegaly (Fig. 12.5). 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

Table 12.5 Antenatal investigations of the mother and the hydropic fetus

Maternal investigation	Fetal investigations
Blood sample	Blood sample
Blood cell count	Blood cell count
Blood group and Rh, Hb electrophoresis	Blood group and Hb electrophoresis
Kleihauer–Betke test	Antibodies
Oral glucose tolerance test	Coombs test
Clotting screen	Infection screening
Erythrocytic enzymes (e.g., G6PD)	Chromosome analysis
Autoantibody screen (anti SSA/SSB)	Conventional karyotyping and microarray
Infection screening	CVS, amniocentesis
Clinical history	Imaging
Karyotype	Detailed anomaly scan
	Fetal echocardiography
	Amniotic fluid index
	Placental morphology
	Doppler flow velocity studies
	Fetal effusion studies
	Biochemistry (e.g., AFP level, specific metabolic tests)
	Viral screen

CVS chorionic villus sampling, *AFP* alpha fetoprotein
Modified from Refs. [218, 219]

Table 12.6 Postnatal investigation of the hydropic neonate

At birth	At necropsy
Maternal clinical history	Review of medical records
Blood sample	Blood sample
Blood cell count	Biochemical and enzyme analysis in metabolic disease
Blood group	Skin/placenta for fibroblast culturing
Hb electrophoresis	Chromosomal analysis
Antibodies	Molecular and enzyme analysis in metabolic disease
Clotting screen	Photographic documentation
Liver function test	X-ray
Infection screening	External examination
Fetal karyotype	Including weight
Fibroblast/cultured cells	Body measurements
Chromosome analysis	NB: some of the measurement may be unreliable in severe hydropic cases
IEM screening	Internal examination
DNA storage	Malformations
Imaging	Lung weights
Echocardiography	Placenta examination
Other radiological examinations	Tissue samples
Fetal measurements	Bacterial and viral cultures
Length	Electron microscopic analysis
Weight	Histology of main organs
Head circumference	Bones (skeletal dysplasia)
Foot length	Skeletal muscle (neuromuscular disease)
Effusion studies	Frozen tissue storage
Viral culture	Piece of the spleen or liver for probable future molecular analysis
Biochemical analysis	

IEM inborn error of metabolism
Modified from Refs. [218, 219]

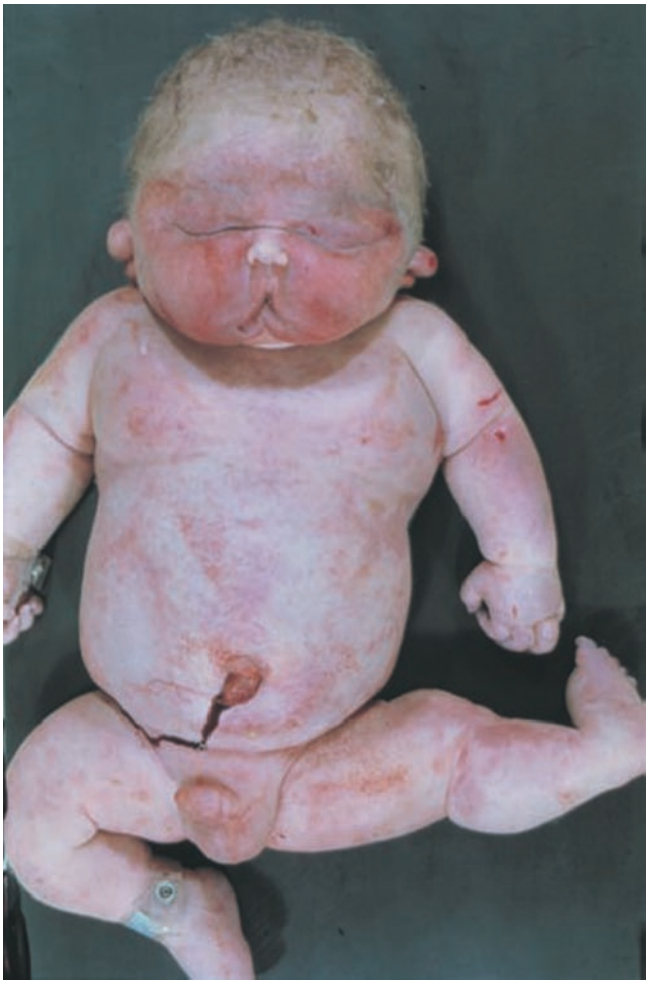

Fig. 12.2 Pale fetus with generalized subcutaneous edema of the head, trunk, and limbs. Facial deformity secondary to edema

or extensive angiomata (Fig. 12.6), indicating the underlying causes of the hydropic state.

Postmortem X-ray examination of the fetus is not only useful to identify the soft tissue shadowing of the expanded edematous tissue but to highlight internal organ calcification (suggestive of congenital infection) or features of skeletal dysplasia (Fig. 12.7).

If consent for a full autopsy is not available, postmortem magnetic resonance imaging (MRI) is a noninvasive investigation that may be more acceptable to some families (see Chap. 5).

Internal

Postmortem examination of fetal hydrops should include a thorough systematic examination combined with ancillary investigations (Table 12.6) [218, 219]. This approach is most important in cases where an antenatal diagnosis has not been made or when all relevant examinations have not been com-

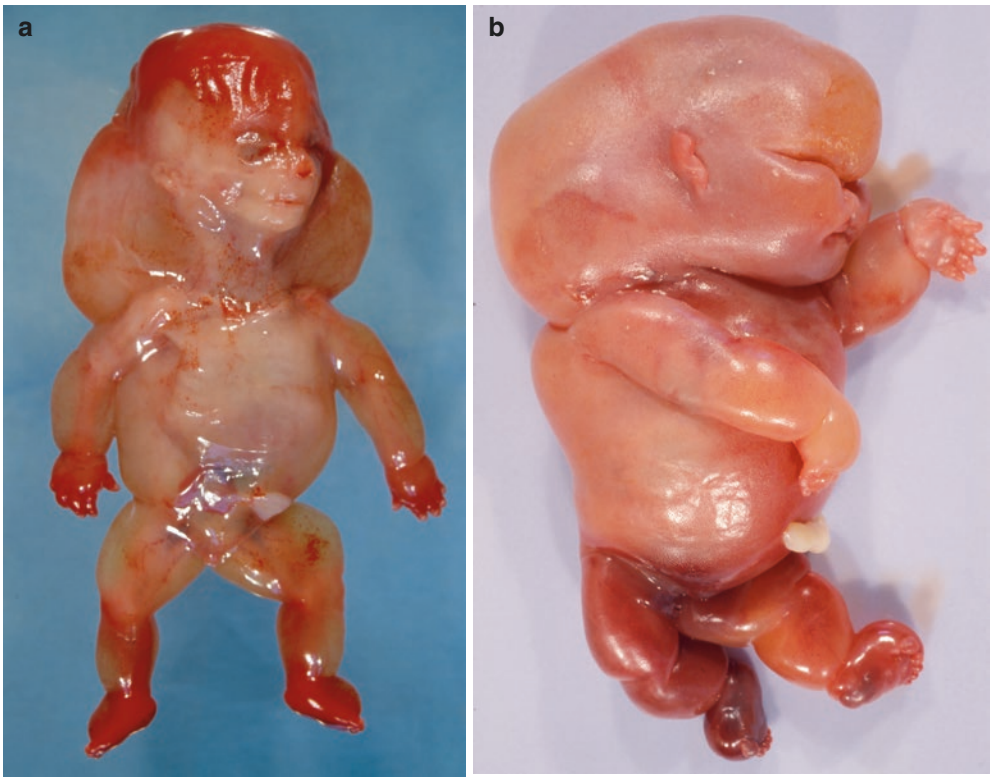

Fig. 12.3 (**a**) 45XO fetus with generalized subcutaneous edema and marked nuchal expansion. (**b**) Another 45XO fetus, later gestation, with generalized edema extending onto the hands and feet. Note the anterior displacement of the ear by the nuchal edema fluid

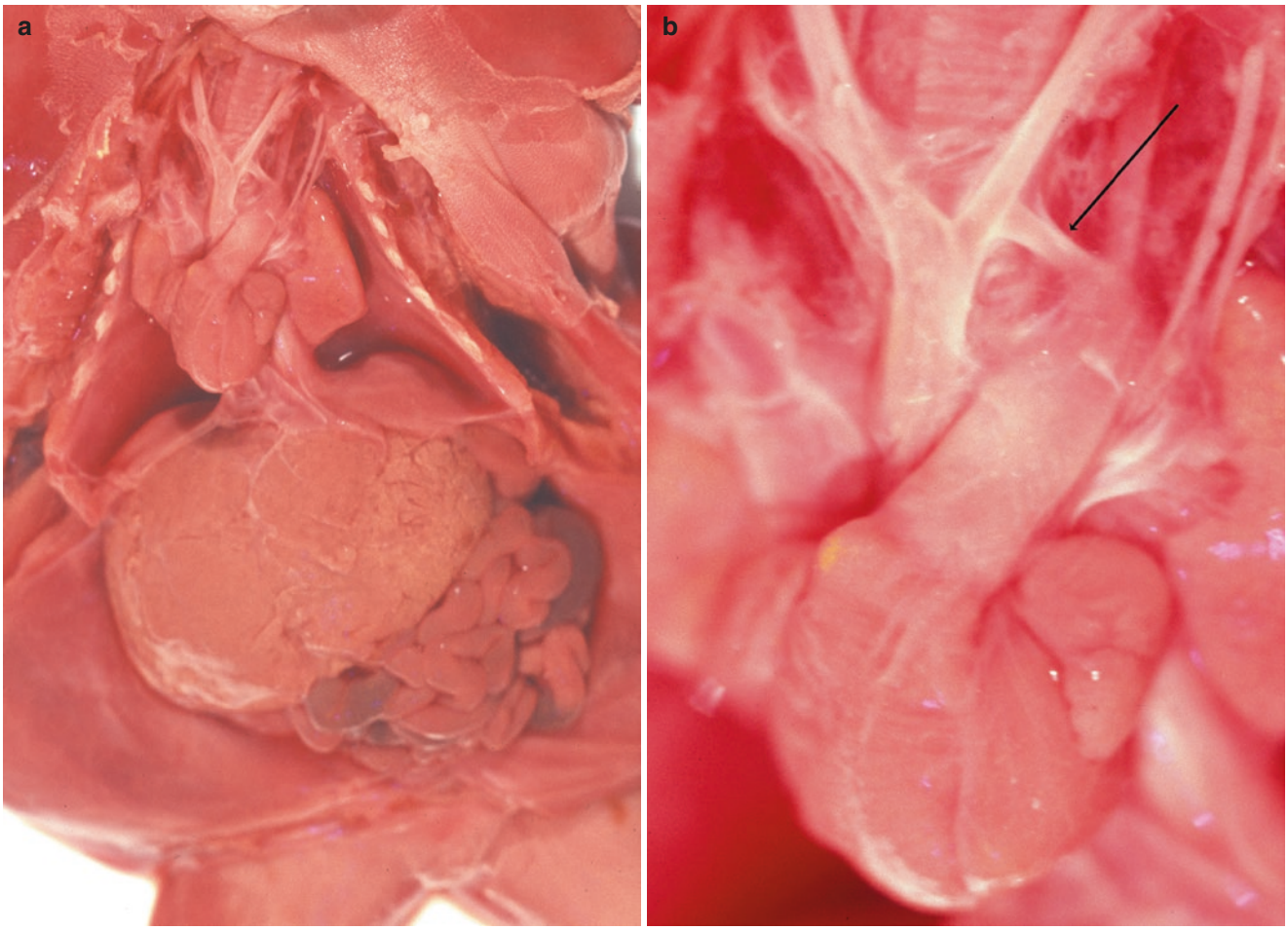

Fig. 12.4 (**a**) Hydropic fetus with 45XO karyotype. The pleural and peritoneal cavities are expanded due to serous fluid accumulation, compressing the lungs and intestines. (**b**) The pulmonary trunk is larger than the ascending aorta; the distal part of the aortic arch is very narrow (tubular hypoplasia)

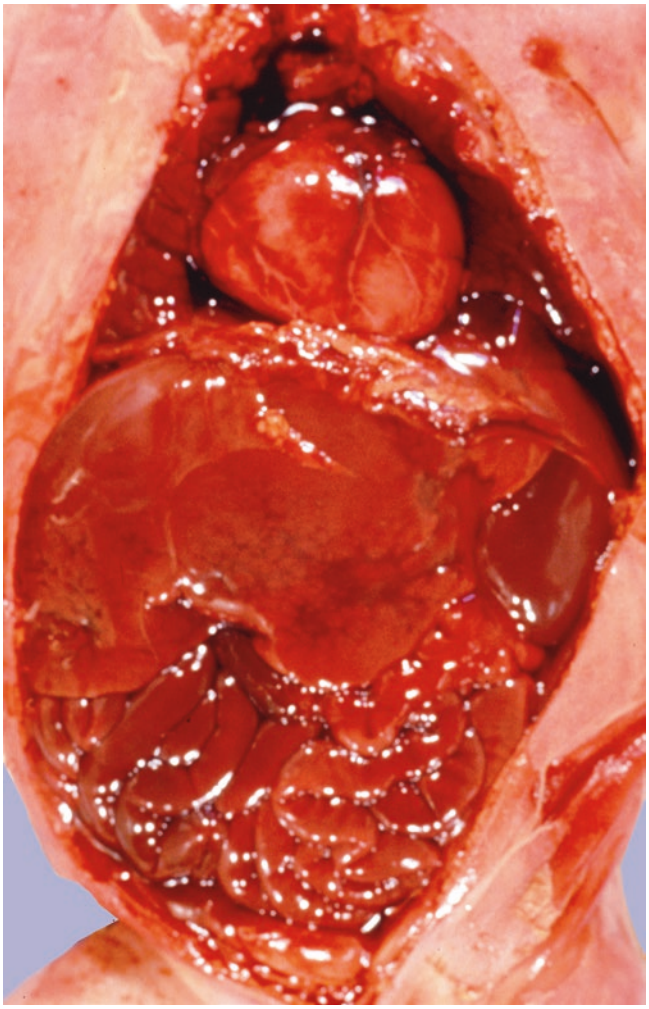

Fig. 12.5 Fetal hydrops due to severe rhesus incompatibility. Massive hepatosplenomegaly is the result of increased erythropoiesis

pleted satisfactorily. Complex malformation syndromes can be technically very challenging and further complicated by secondary changes of maceration or the small size of some fetuses.

Upon opening the body cavities, serous fluid collections should be sought, recorded, and measured, if possible. It is usual to find an excess of fluid in all body cavities, 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. In a review of fetal ascites, Machin [221] found that many of the associations of fetal ascites were also associated with generalized hydrops, although there was an excess of intra-abdominal abnormalities such as urinary tract obstruction and gastrointestinal or hepatic abnormalities. A very large pericardial effusion is unusual unless there is intrapericardial pathology such as teratoma [186] (Fig. 12.8) or cardiac diverticulum [78].

Mild subcutaneous edema is often observed when intrauterine death has occurred and its significance is dubious. Postmortem fluid accumulation in serous cavities could be distinguished from significant ascites by its dark red color.

The pleural effusions of some duration not only cause some degree of pulmonary hypoplasia but also affect lobar contour, with loss of concavity of the inferior surface of the lower lobes and an acute angle of the inferior border (Fig. 12.9).

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.

As malformations are among the most common causes of hydrops, these should be specifically looked for. In the thoracic cavity, congenital heart disease, pulmonary anomalies (Figs. 12.10, 12.11, 12.12, and 12.13), and intrathoracic masses (Figs. 12.8, 12.14, and 12.15) should be sought. These are also associated with mediastinal shift with compression of the contralateral lung and even the great vessels.

Intra-abdominal causes include tumors (Figs. 12.16 and 12.17), cystic kidneys, lower urinary tract obstruction with dilated bladder, and genital organ malformation (e.g., hydrometrocolpos). Intestinal pathology includes atresia and volvulus with hemorrhage and infarction.

The heart and liver are often enlarged even if they are structurally normal (Fig. 12.5). Cardiomegaly may be a compensatory reaction to heart failure. Taweevisit showed [222] that hepatomegaly in anemic hydrops cannot be purely explained by extramedullary hematopoiesis but speculated that the major factor is congestion due to high cardiac output and cardiac failure due to anemia. The hepatosplenomegaly is due to persistent hepatic extramedullary hematopoiesis or infiltrative processes. The former is secondary to intrauterine stress with increased demand on bone marrow elements. Such stressors include anemia (Fig. 12.6), bleeding, congenital infections, hypoxia, and congenital defects [224]. Alternatively, persistent extramedullary hematopoiesis may be due to reduced bone marrow space, such as in osteochondrodysplasias. The infiltrative processes include storage disease and familial hemophagocytic lymphohistiocytosis [146].

Intracranial pathology includes congenital infections and tumors, vascular malformations, and structural defects, presented with hydrocephalus, hemorrhage, necrosis, and calcification (Fig. 12.18).

Late disruptive defects, both intra- and extracranial, resulting from hypotensive ischemia or embolic phenomena, should be sought in monochorionic twins [225].

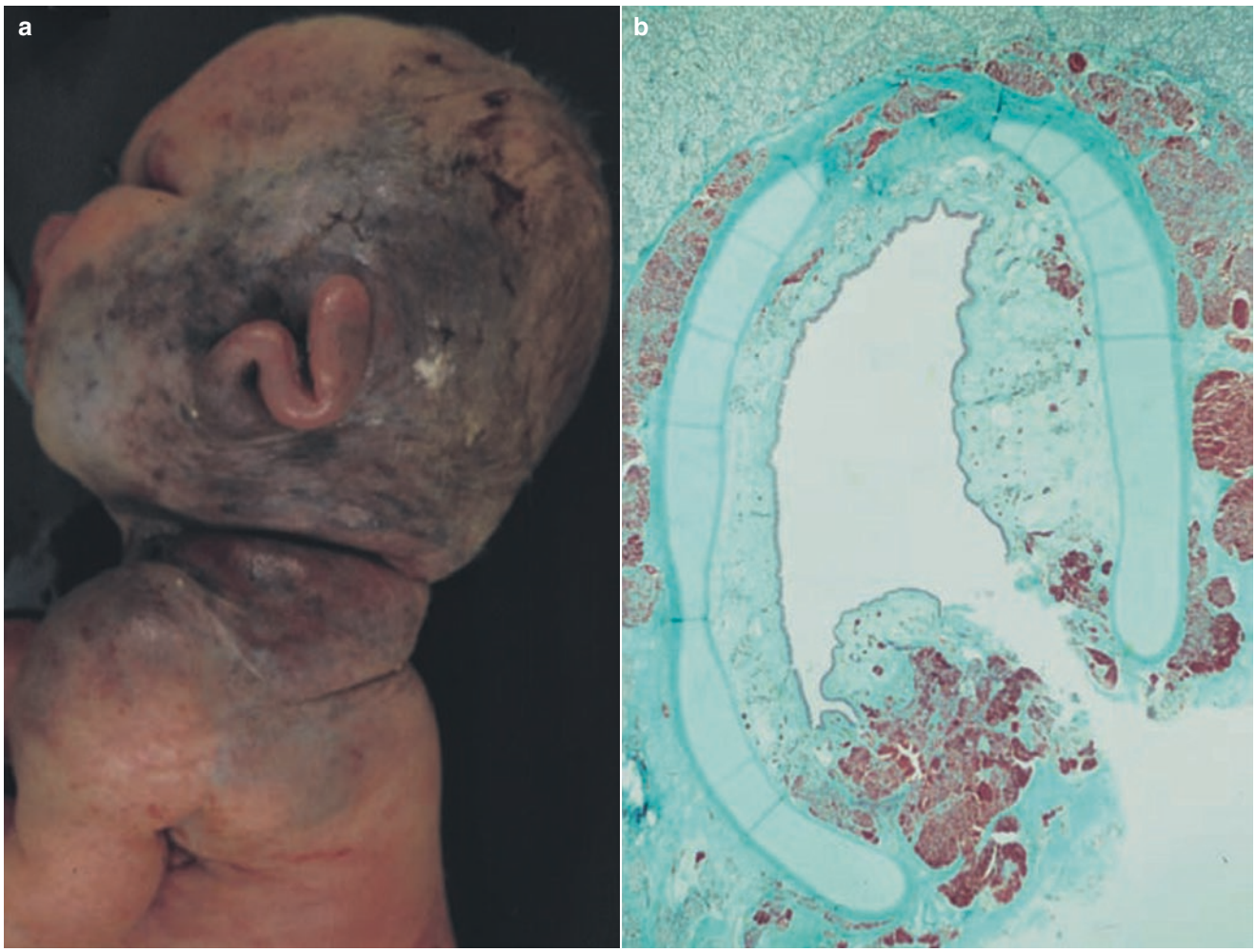

Fig. 12.6 (**a**) Hydropic stillbirth with a large angioma involving the left side of the face, head, and shoulder. (**b**) The angioma involving the laryngeal mucosa and the surrounding soft tissue

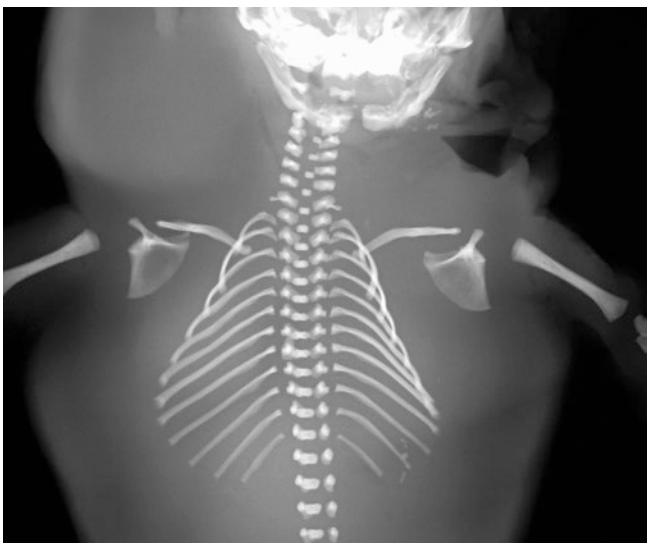

Fig. 12.7 Postmortem radiograph of a fetus with 45XO karyotype showing marked soft tissue expansion due to edema. Note the bilateral cervical ribs

Fig. 12.8 Cardiac teratoma arising from the root of the heart. Pericardial sac is markedly enlarged (upon opening was filled with serous fluid)

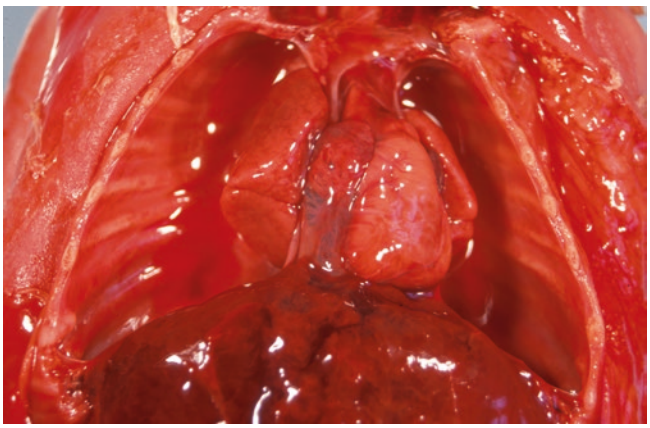

Fig. 12.9 Large bilateral pleural effusions with secondary severe pulmonary hypoplasia

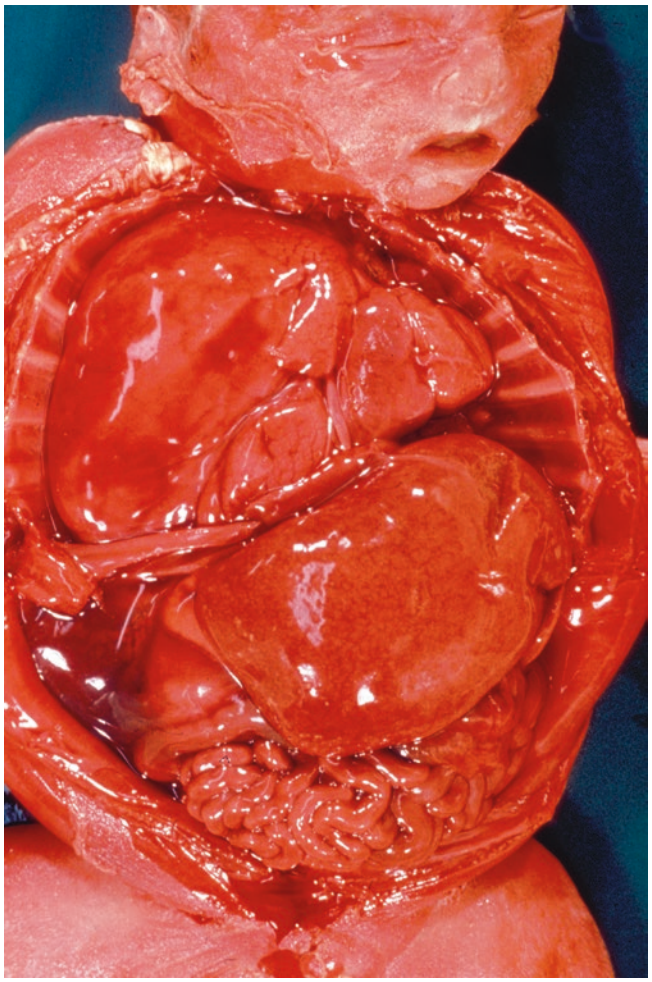

Fig. 12.10 Hydropic macerated stillbirth: congenital cystic adenomatoid malformation of right upper lobe of the lung with mediastinal shift and displacement of the liver to the left. Right depressed hemidiaphragm [223]

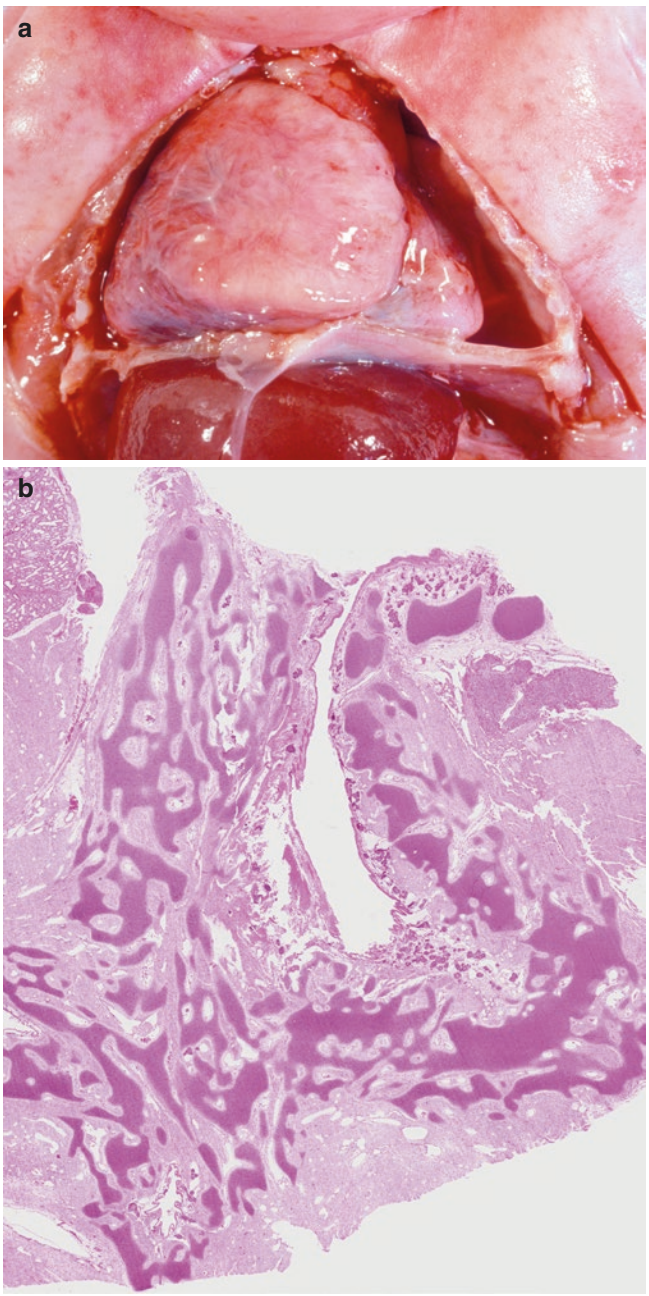

Fig. 12.11 (**a**) Mesenchymal hamartoma replaces the right upper lobe of the lung. (**b**) Hamartoma comprised irregular bars of cartilage and myofibroblastic tissue

Histology

Routine sampling of organs for histological examination should be undertaken (see Chap. 2) even when a gross abnormality thought to be causally related to the hydrops has been identified. Histological appearances of the heart and lungs

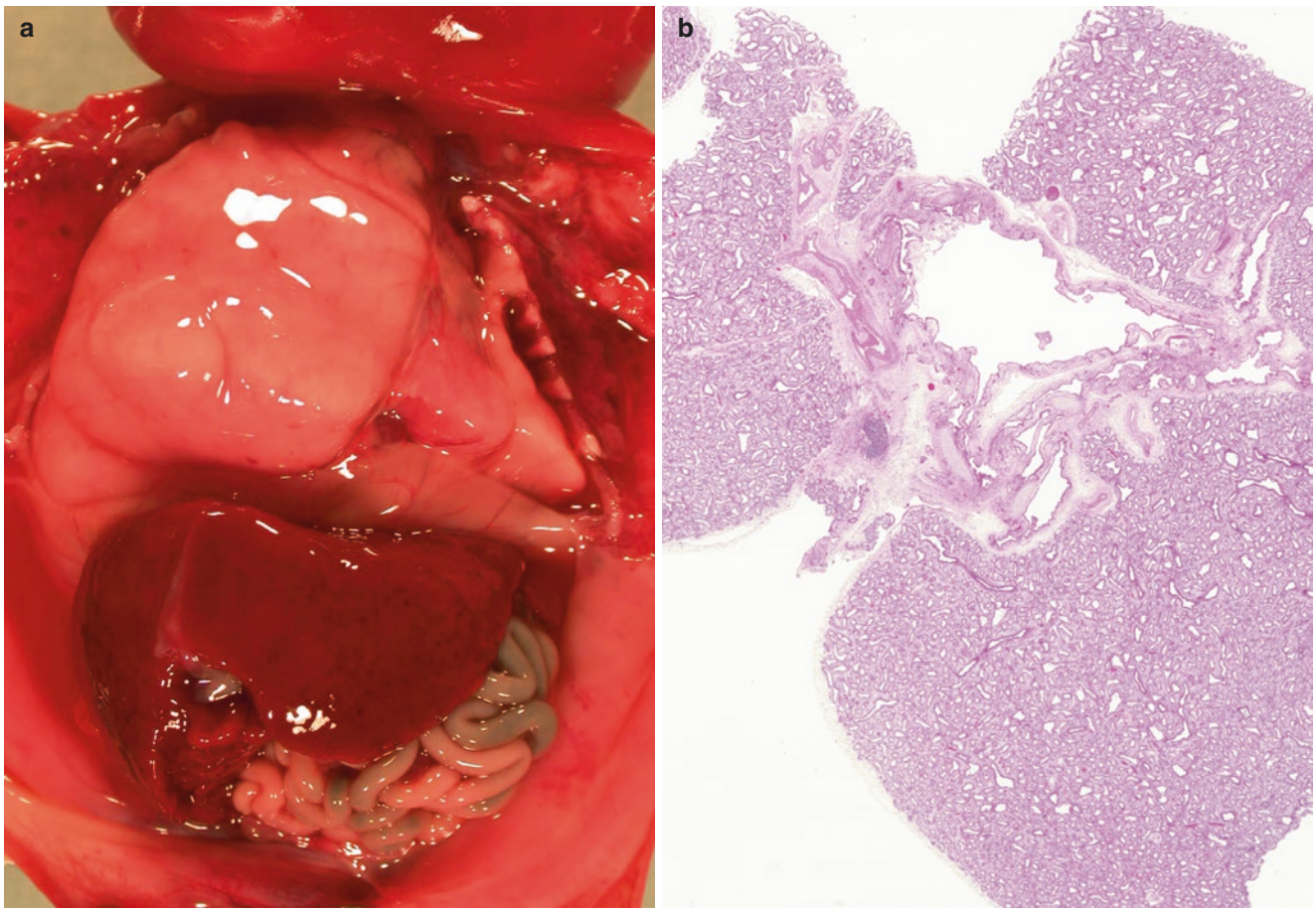

Fig. 12.12 (**a**) Expansion of the right middle and lower lobes of the lungs due to bronchial atresia. Note the mediastinal shift and hypoplasia of the left lung and right upper lobe. (**b**) Dilated proximal bronchi with loss of the cartilage in their walls and with parenchymal hyperplasia

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. 12.19). This may sometimes be informative in antenatally detected fetal arrhythmias and in cases where there is a maternal history of lupus. The myocardium may show evidence of infection, infarction, calcification, fibrosis, intracytoplasmic megamitochondria, or vacuolations. 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. 12.15). In such cases, other features of tuberous sclerosis should be sought.

Space-occupying lesions, either in the chest or in the abdominal cavity, should be examined, and their contribution to mechanism (e.g., compression on great vessels, high cardiac output) of hydrops can be established. 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 can be confirmed with immunohistochemical panel. Assessment of lymphatics was also suggested by Bellini especially in idiopathic nonimmune hydrops cases [3].

The adrenal glands may show adrenocortical cytomegaly, especially the ones associated with Hb Bart hydrops fetalis [226]. However, adrenocortical cytomegaly is a nonspecific finding and reflects a cellular adaptation to an intrauterine stressful environment. Therefore, it can be seen in various conditions, including congenital rubella infections and various congenital malformation syndromes (e.g., Beckwith–Wiedemann syndrome) [22].

In certain situations, examination of the vessels may reveal the underlying cause (Fig. 12.20). The presence and the distribution of the soft tissue calcification on the X-ray

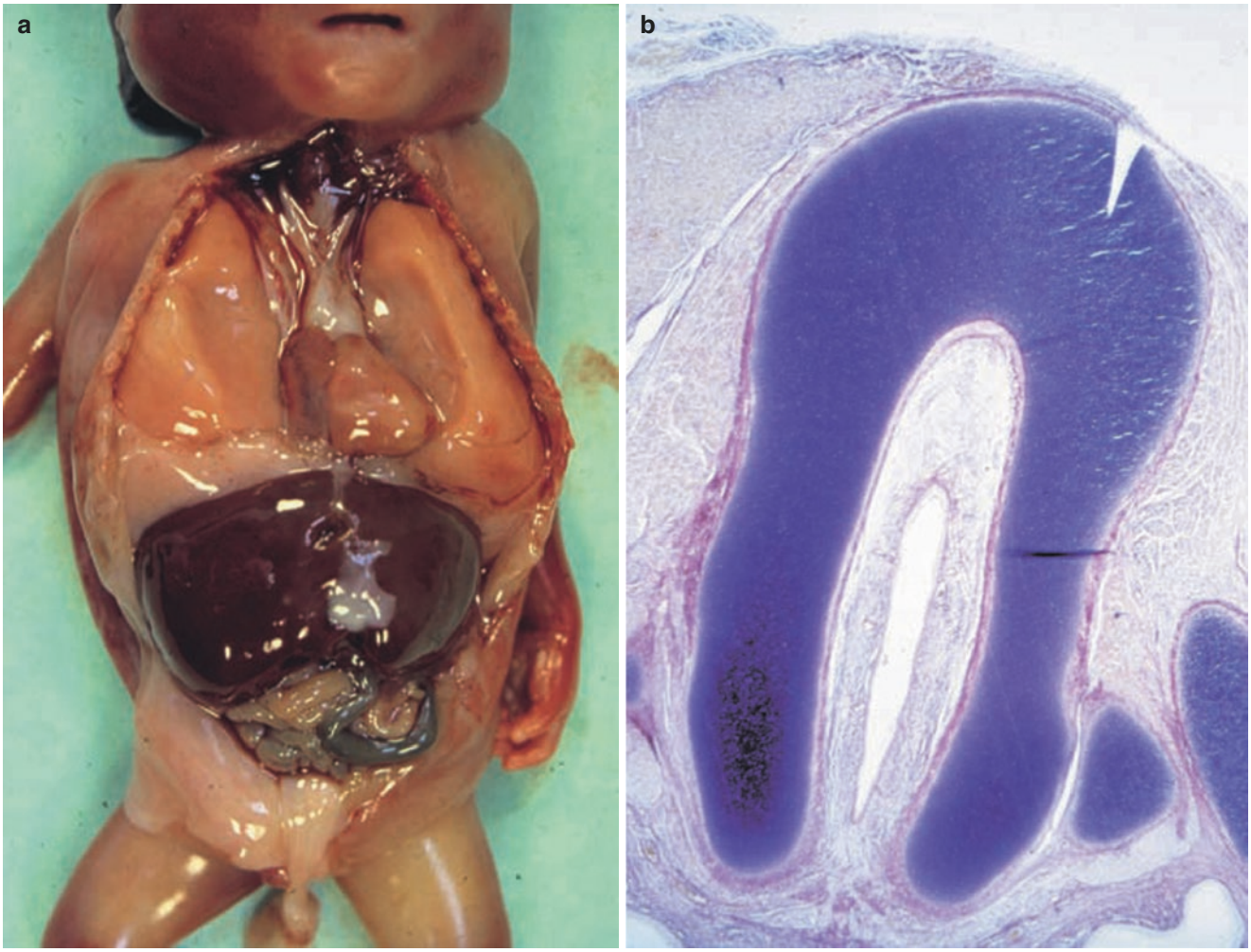

Fig. 12.13 (**a**) Fetus of 20 weeks' gestation. Massive distention of both lungs, depressing the diaphragm. (**b**) Severe laryngeal stenosis due to anomalous development of the cartilaginous structures, reducing the lumen to a slit [223]

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 or malformations.

Congenital fetal infection can be presented with typical histological appearance (e.g., intranuclear or intracytoplasmic inclusions) or can be confirmed with more specific investigations including immunohistochemistry or in situ hybridization (Fig. 12.21).

The Placenta

Fetal hydrops may be accompanied by edema of the placenta and umbilical cord. These changes may be focal and not uniformly distributed. On gross examination, the placenta is often extremely thick and heavy, pale, and friable. It may weight more than 1000 g. Similar changes can be seen when there is an intra-abdominal mass obstructing the venous return from the placenta. In congenital nephrotic syndrome, placental edema can be prominent, even when the fetus is only mildly affected. In other cases, however, the placenta may appear normal even when the fetus is severely hydropic in high-output heart failure or some chromosome anomalies.

In twin to twin transfusion syndrome seen in monochorionic, diamniotic twin placentation, there may be a marked difference in appearance between the territories of the placenta related to each baby. The donor portion is usually pale, friable, and often thicker than that related to the recipient, which is often intensely congested (Fig. 12.22). Vascular communications between the two circulations can be demonstrated by injection studies, but the clinically significant vascular shunting takes place within the deep placental parenchyma.

Histologically, the placenta is very hydropic with relative villous immaturity with presence of nucleated red blood cells in the fetal vessels. Mineralization of the trophoblastic basement membranes is a nonspecific finding that is usually found in hydrops. Other features are related to the underly-

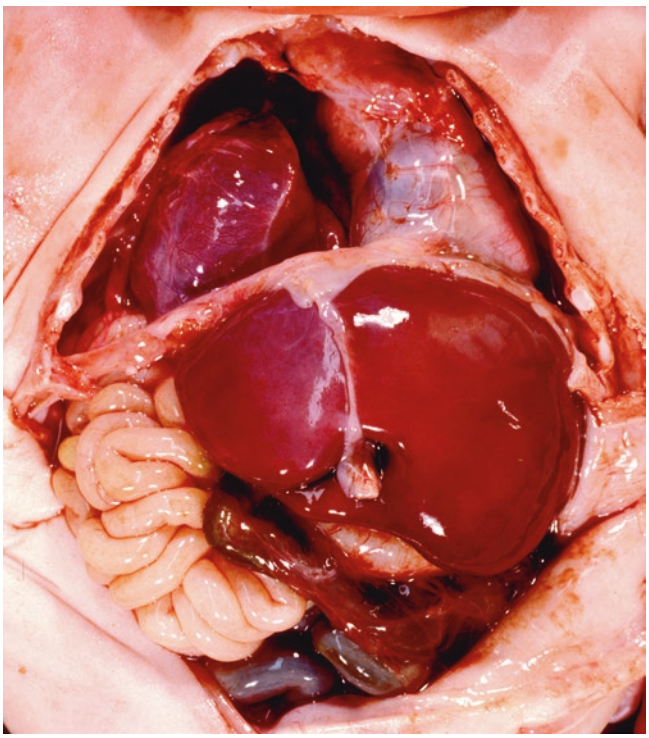

Fig. 12.14 Herniation of the right lobe of the liver via right-sided diaphragmatic defect into the right hemithorax, displacing the heart and lungs to the left and leading to fetal hydrops and polyhydramnios [41]

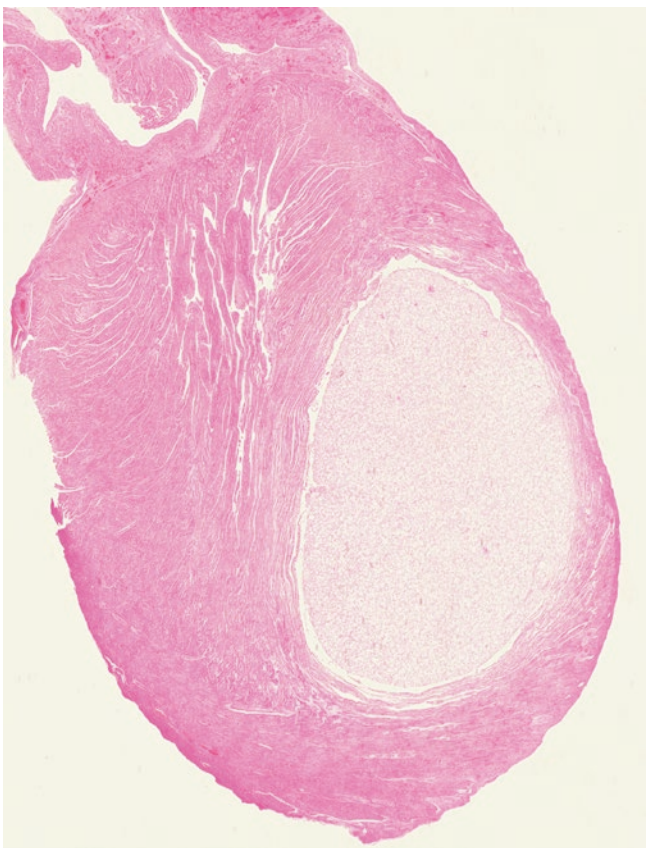

Fig. 12.15 Rhabdomyoma of the cardiac interventricular septum

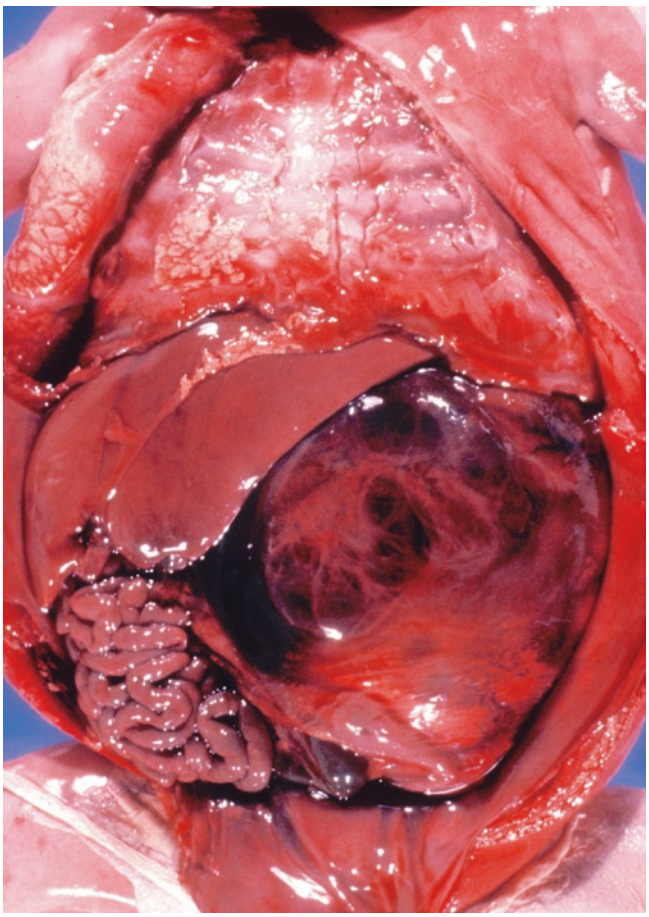

Fig. 12.16 Congenital mesoblastic nephroma of left kidney, displacing the intestines and the liver to the right. Also obstructing the systemic venous return leading to hydrops

ing pathology (e.g., chronic villitis and viral inclusions in congenital infections, chorangioma; Fig. 12.23). In congenital nephrotic syndrome, the villi may be uniformly edematous and Hofbauer cells are readily seen. In rhesus disease, villous hydrops is not usually gross and is patchy in distribution with many villi that are of normal in size. There is persistence of cytotrophoblast so that villi appear immature. Careful examination of the non-hydropic villi shows plugging of villous capillaries by clumps of erythropoietic cells (Fig. 12.24). In the fetus with neuroblastoma, similar capillary plugging by clumps of tumor cells is seen (Fig. 12.25). Prominence or increased size of trophoblast cells with cytoplasmic vacuolation is present in some fetuses with genetic metabolic disease (Fig. 12.26).

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.

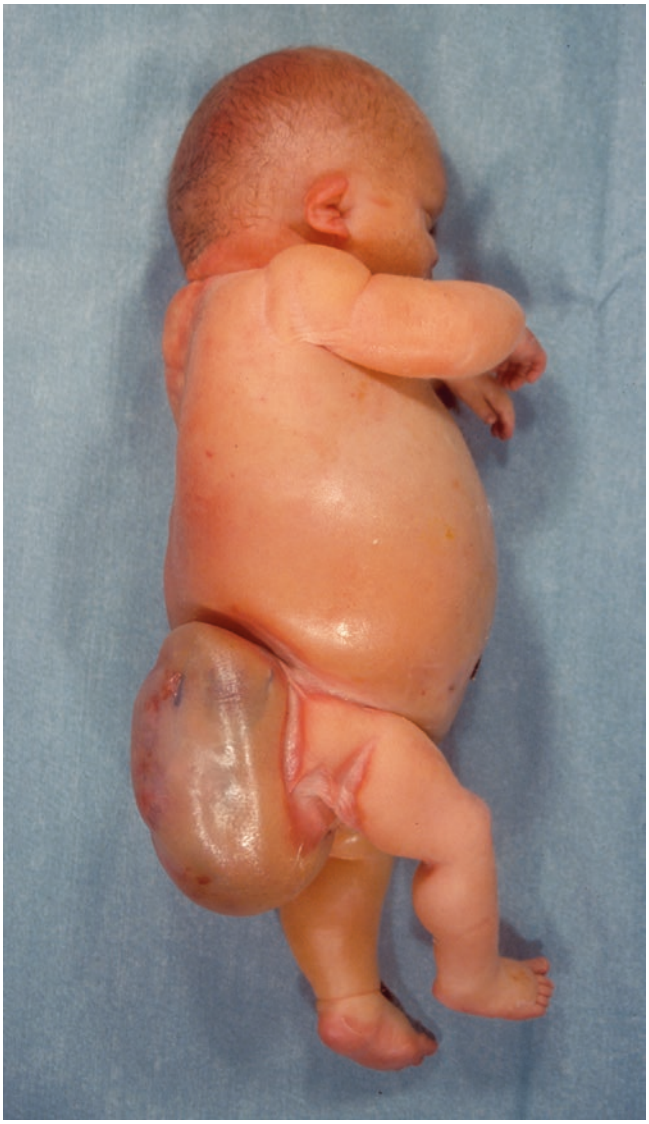

Fig. 12.17 Hydropic neonate with sacrococcygeal teratoma with a large intrapelvic component

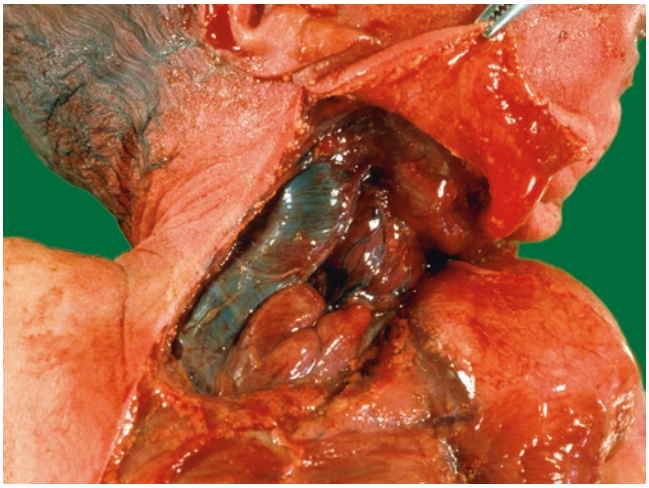

Fig. 12.18 Meningeal angiodysplasia leading to enlarged jugular vein (demonstrated on the photo) resulting in a state of high cardiac output

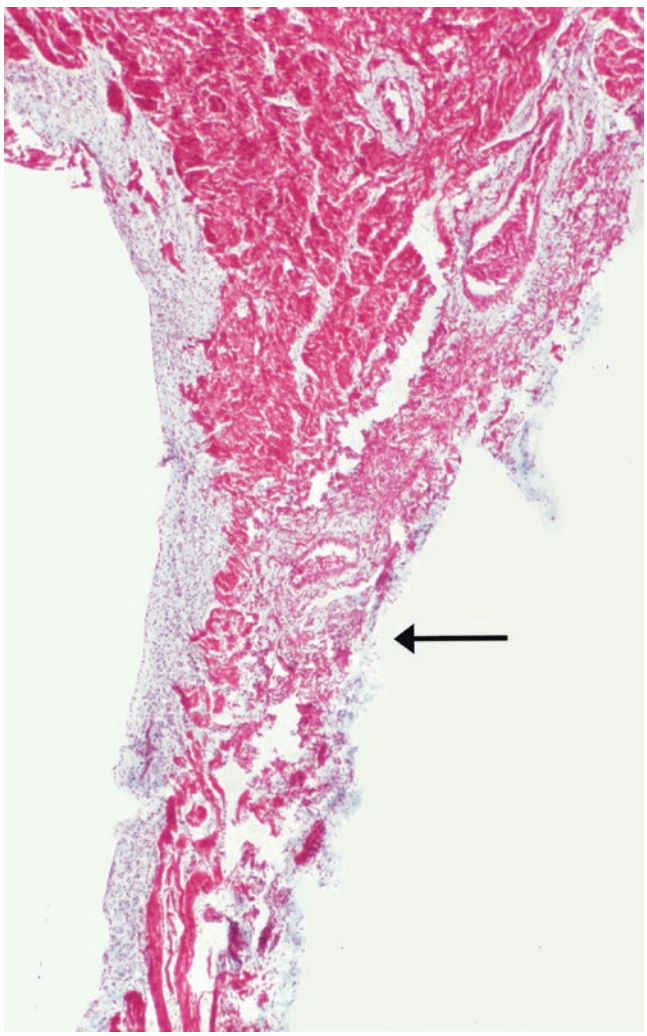

Fig. 12.19 Right atrial wall with a hypoplastic sinoatrial node (*arrow*) with a central sinus node artery (Masson's trichrome)

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, as the development of hydrops is often seen as a poor prognostic feature, particularly in conjunction with complex structural heart defects [227, 228].

Among the earliest types of prenatal therapy tested were antiarrhythmic drugs, such as digoxin or beta-blockers administered to the mother, in cases of fetal arrhythmia [178, 229, 230]. Digitalization was also useful in a case of severe aortic stenosis with endocardial fibroelastosis at 27 weeks and resulted in the resolution of hydrops and a live-birth delivery at term [231]. Digoxin has also been useful in the management of cystic adenomatoid malformations of the

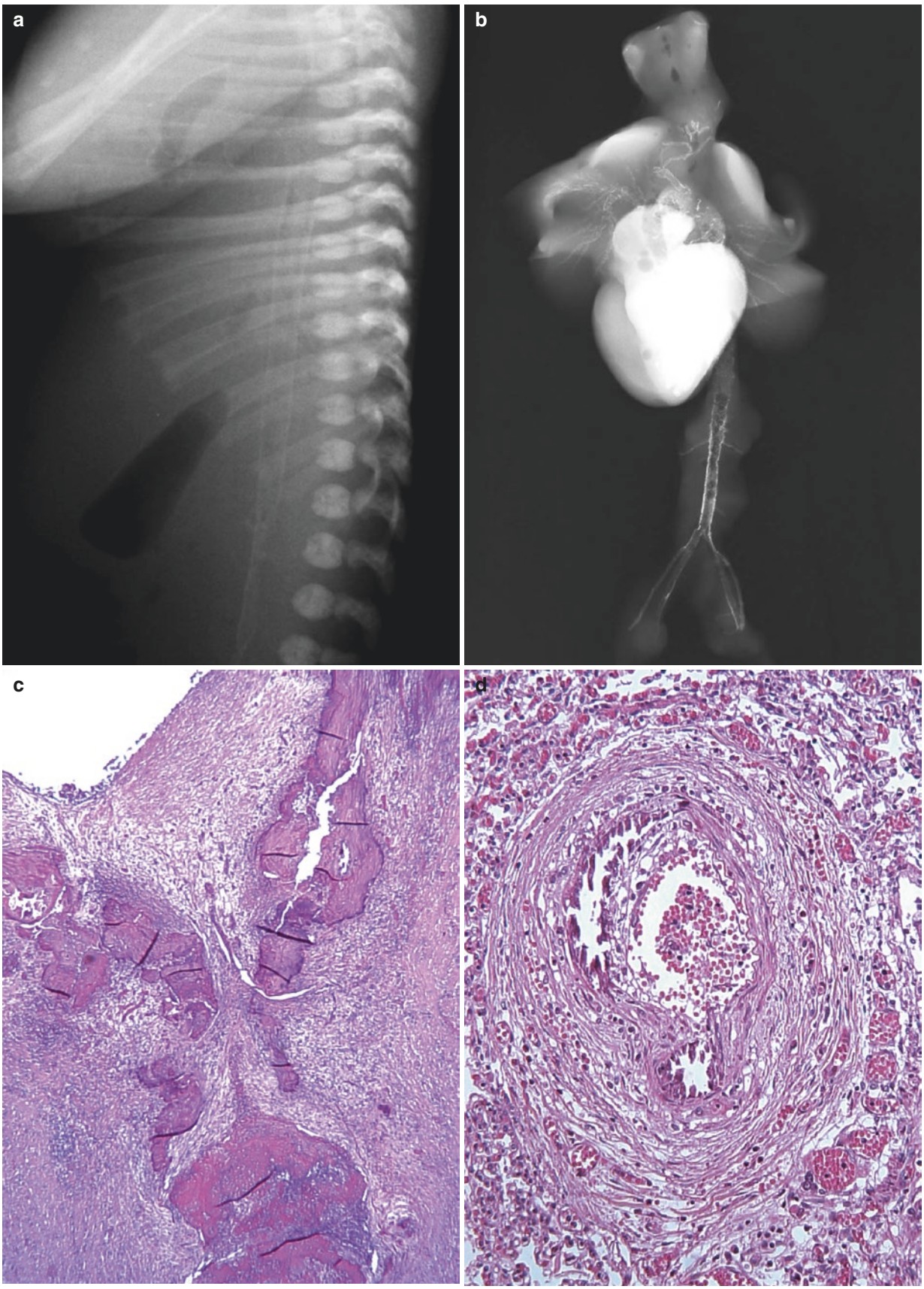

Fig. 12.20 (**a**) Lateral radiograph of a hydropic stillbirth with diffuse calcific arteriopathy. The aorta is outlined on the film owing to excessive mineralization. (**b**) Postmortem radiograph of the dissected organ block (from a similar case) showing calcification within the pulmonary, renal, and mesenteric arteries. (**c**) Heavily calcified proximal pulmonary arteries. (**d**) Mineral deposits partially replacing the internal elastic lamina (distal branches of pulmonary arteries)

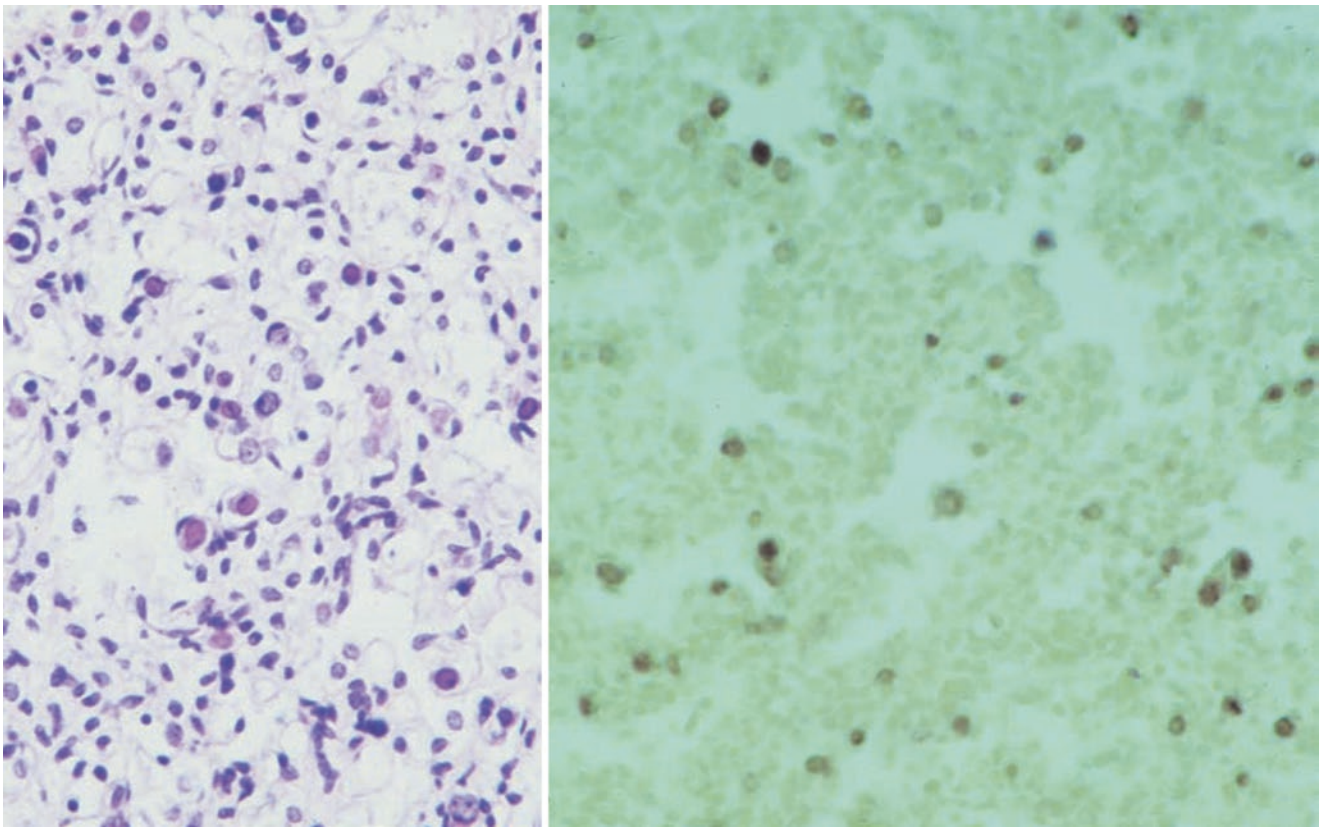

Fig. 12.21 Parvovirus infection. (**a**) Intranuclear inclusions in pulmonary capillary endothelial cells. (**b**) In situ hybridization demonstrates a large number of infected cells

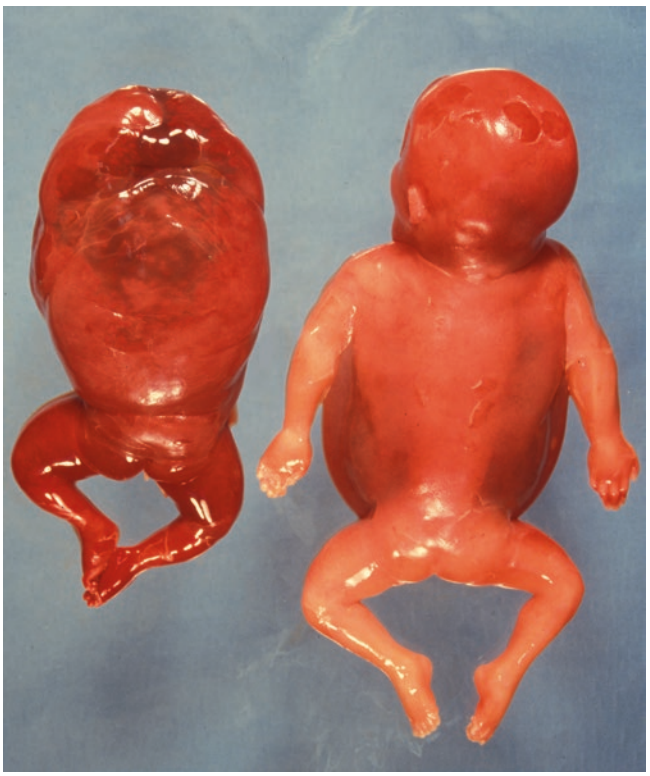

Fig. 12.22 Acardiac twin (*left*) is plethoric; pump twin (*right*) is anemic and hydropic

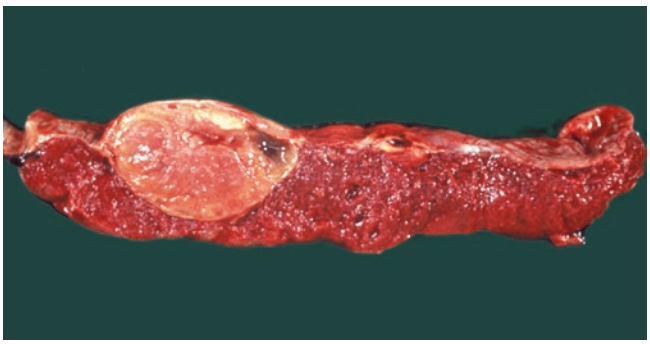

Fig. 12.23 Large chorangioma in the placenta from a pregnancy complicated by third trimester fetal hydrops and polyhydramnios

lung (CCAM) in conjunction with neonatal surgery [232]. In cases of fetal tachycardia (reentrant supraventricular, junctional ectopic, or ventricular) refractory to digoxin, the addition of maternal oral amiodarone can be effective in fetal hydrops and/or ventricular dysfunction [233]. Antiarrhythmic drugs, including digoxin, have been given to fetuses directly to counteract the often poor or unpredictable placental drug transfer that may occur in the hydropic fetoplacental unit [234, 235]. Direct fetal therapy with amiodarone may benefit supraventricular tachycardia and atrial flutter in hydrops, and its use reduces the number of repeat administrations required

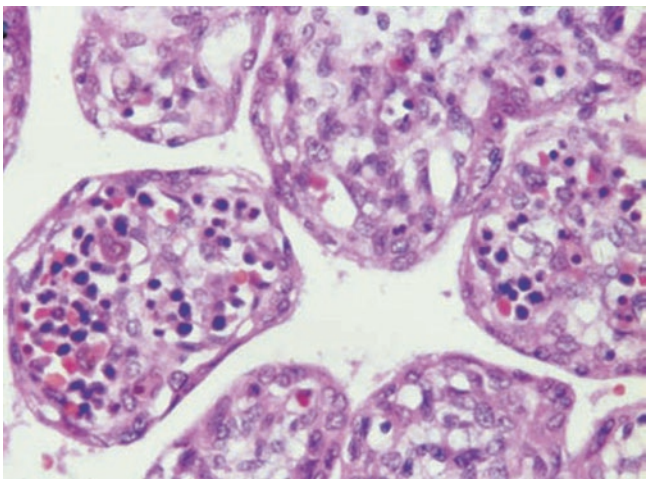

Fig. 12.24 Immune hydrops (rhesus). Placenta with nonuniform hydropic changes. Capillaries of non-hydropic villi are plugged by erythropoietic cells

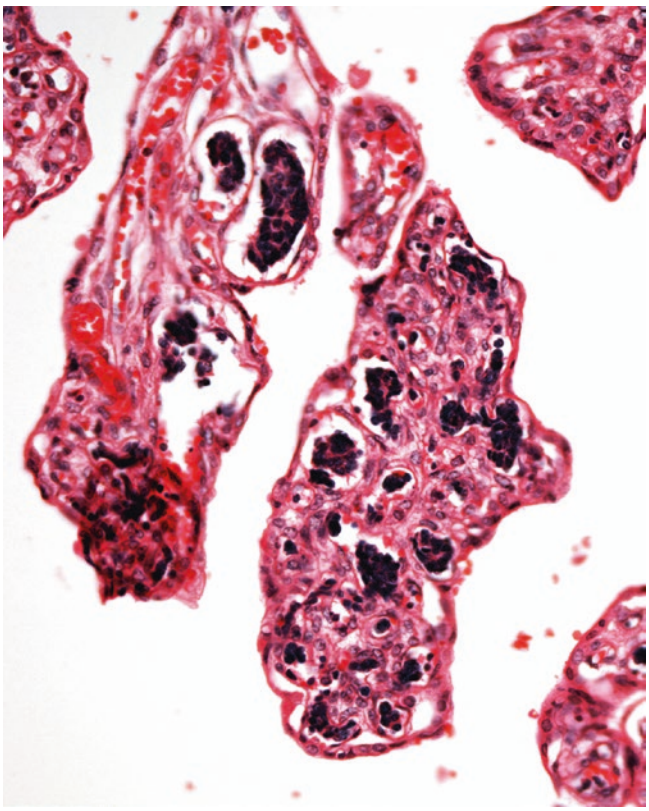

Fig. 12.25 Hydropic fetus with neuroblastoma. Tumor emboli are present within villous capillaries in the placenta

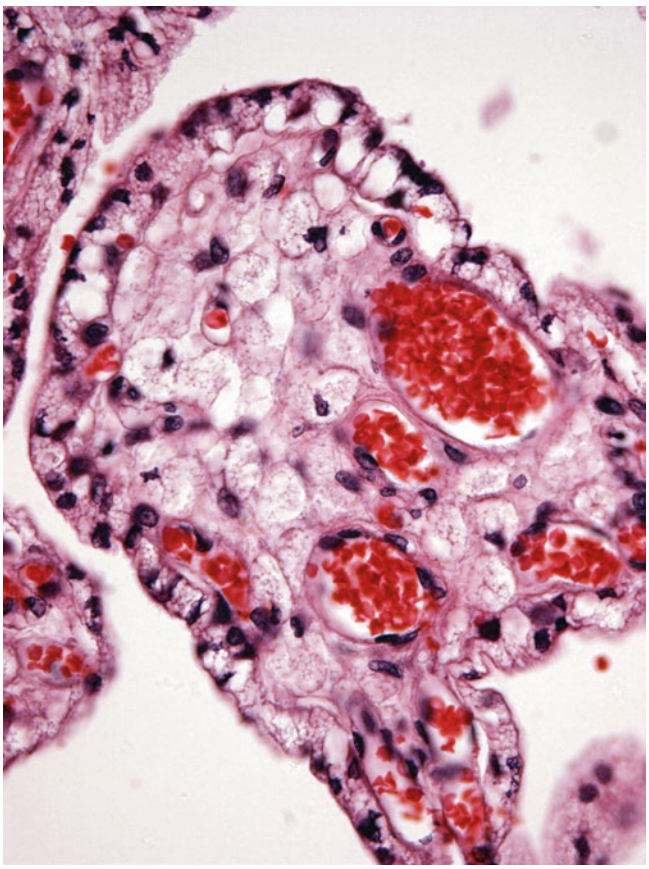

Fig. 12.26 Metabolic storage disease (sialidosis). Prominent, vacuolated trophoblast and Hofbauer cells

owing to its prolonged elimination half-life [236]. Autoimmune-associated atrioventricular block has been managed by immunoadsorption of maternal anti-Ro/SSA antibodies [237]. Other drugs, particularly corticosteroids, may have utility depending on the etiology of hydrops. Hydrops due to cystic adenomatoid malformations of the lung (CCAM), including in Stocker type III—usually the most difficult type to manage—has been observed to resolve following the administration of betamethasone [238–240]. It has been speculated that the response to such therapy owes its effect to a degree of lesional maturation or involution [239]. Steroid medication [241] and aggressive amnioreduction [242] may have a role in the management of twin transfusion with hydrops.

An emerging modality in fetal cardiac intervention 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 [243].

Thoraco-amniotic drainage of pleural effusions/chylothorax or large cysts [244, 245] to encourage lung growth is now relatively frequently undertaken, with survival (57 %) in one study limited mainly by premature labor [246]. Successful outcomes have also been achieved with a similar approach in pulmonary sequestration [247, 248]. Pericardiocentesis and thoraco-amniotic shunting to relieve tamponade have been

performed with intrapericardial teratomata enabling tumor resection in the neonate [249, 250]. Likewise, drainage of ascites or the urinary bladder in order to reduce intra-abdominal pressure may be beneficial.

Open fetal pulmonary lobectomy for CCAM has been successful with a fetal survival rate of about 50–60 % [250]. A relatively new surgical procedure known as EXIT (ex utero intrapartum) is beginning to enable salvage of hydropic fetuses with congenital high airway obstruction (CHAOS) [252, 253].

Hydrops is an indication in some centers for intervention in cases of sacrococcygeal teratoma owing to high fetal mortality rates.

Percutaneous drainage of large cysts may alleviate dystocia at delivery and can decompress the renal system in cases where there is a cystic intrapelvic component. Prenatal open total or partial resection of the tumor has been performed in a small number of reported cases but may give way in the future to feeding vessel ablative therapy or fetoscopic resection to limit the risks to the mother and fetus of mid-gestation hysterotomy [254]. Fetal blood transfusion and albumin infusion have been used in various circumstances such as parvovirus B19 infection [255, 256], ascitic/hydropic RhD alloimmunization [257], and idiopathic hydrops [258].

Radiofrequency ablation of the blood flow to an acardiac twin was an effective therapy for the hydropic pump twin [259] as was alcoholization of the feeding vessel of a placental chorangioma [260]. Sclerotherapy with OK-432 was of benefit in an enlarging cystic hygroma [261].

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