Hydrops fetalis is an end-stage process for a number of different diseases. It is defined as an abnormal accumulation of interstitial fluid in at least two body cavities (pleural, peritoneal, or pericardial) or one body cavity in association with anasarca (generalized massive edema). Placentomegaly and polyhydramnios are common findings in cases of hydrops but are not needed for the diagnosis.

Lymphangiectasia, which is abnormal dilatation of the lymphatic vessels, should not be mistaken for hydrops. In the first trimester, general body wall lymphangiectasia can have a “space suit” appearance (Fig. 41.1) due to the fluid in the skin and/or subcutaneous tissues. The finding has a poor prognosis, with 26 in 30 prospectively identified cases in the first trimester having abnormal karyotype.1 However, because there is not typically fluid in other body cavities, this is not hydrops.

Hydrops is the late stage of many processes that lead to redistribution of body fluids among the intravascular and interstitial compartments. This imbalance of fluid can have many causes (Table 41.1). There are at more than 150 different causes of fetal hydrops. Many of the causes and associations with hydrops overlap. The basic etiology of hydrops is an imbalance of interstitial fluid, which may be caused by myocardial failure, high-output cardiac failure, decreased colloid oncotic plasma pressure (anemia), increased capillary permeability, and/or obstruction of venous and lymphatic flow.
Hydrops can be **immune** or **nonimmune** in origin. Immune hydrops is defined by a circulating antibody against red blood cells (RBCs) in the mother, whereas in nonimmune hydrops no such antibody is found. Before the widespread introduction of rhesus (Rh) anti-D immune globulin in the 1970s, most cases of hydrops were immune, whereas about 85% are nonimmune. This chapter reviews the findings of fluid in different body cavities and the causes, diagnosis, and treatment of hydrops. Recent series have reported fetal hydrops mortality rates ranging from 58% to 61%. This improved survival compared to older series is thought to be due to fetal medical and interventional techniques that allow for reversal of hydrops in nonaneuploid cases. Although hydrops is a relatively common indication for tertiary-level fetal evaluation, because of the many causes, each specific etiology is relatively rare.

**SONOGRAPHIC FEATURES**

It is important for clinicians to understand the sonographic appearance of fluid in the different interstitial compartments of the fetus. These fluid collections can occur in isolation, as in isolated **ascites** or isolated **pleural** or **pericardial** effusion. When one collection is seen, it is important to assess for a second collection to make the diagnosis of hydrops; the fluid collection must be in at least two body cavities to qualify as hydrops. Other findings in hydrops can include **subcutaneous edema**, **polymedromnios**, and **placentomegaly**.

**Ascites**

Fetal ascites is diagnosed when fluid is seen between **bowel loops**, along the abdominal flanks, around the liver, and outlining the umbilical vessels (Fig. 41.2). In normal fetuses, a small hypoechoic band (<2 mm in thickness) extending along the anterior and lateral fetal abdomen may be present. This “pseudoascites” represents normal abdominal wall muscles or abdominal wall fat and should not be mistaken for an abnormal fluid collection (Fig. 41.3). The distinction between the pseudoascites appearance and true ascites can be made when the transducer angle is changed and the appearance resolves. Pseudoascites does not surround the liver but rather stops at the insertion of the ribs. Note that true ascites will extend around bowel loops (Fig. 41.4, Video 41.1), whereas pseudoascites is always a subcutaneous finding. Isolated ascites can be an early sign of hydrops. If truly isolated, it can be caused by a urinary or gastrointestinal obstruction. Isolated fetal ascites has a more favorable prognosis than hydrops but requires follow-up to ensure that hydrops does not ensue.

Small collections of ascitic fluid may outline abdominal viscera, including bowel loops or bladder, and may cause an apparent increase in their echogenicity. Larger accumulations outline the liver and spleen (see Fig. 41.2A and D). The umbilical vessels will be seen as parallel echogenic lines traversing the fluid space (see Fig. 41.2C). Bowel loops may be free floating or, when meconium peritonitis is present, may appear as a matted, echogenic posterior mass. In male fetuses, ascitic fluid may track through the patent processus vaginalis into the scrotum, leading to **hydroceles** (Fig. 41.5). Chronic chest compression from massive ascites may result in **pulmonary hypoplasia**.

**Pleural Effusions**

Pleural effusions typically occur later in hydrops than does ascites. If isolated and small, pleural effusions tend to have a benign course (Fig. 41.6A, Video 41.2). A small effusion is seen as a thin, echolucent rim surrounding lung tissue and may also outline mediastinal structures. Small pleural effusions do not shift the mediastinum. Pleural effusions associated with hydrops may be **unilateral** or **bilateral**, often beginning as unilateral collections that progress to bilateral involvement (Fig. 41.6D). If mediastinal shift is visualized in association with a small pleural effusion, a
<table>
<thead>
<tr>
<th>Cause (Percentage of Nonimmune Hydrops)</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular (20%)</td>
<td>Increased central venous pressure</td>
<td>Structural heart disease (hypoplastic left or right heart syndrome, atrioventricular canal) Myocardial or pericardial tumors (rhabdomyoma in tuberous sclerosis) Tachyarrhythmia Bradyarrhythmia (congenital heart block [anti-Rho] or other maternal autoimmune disease)</td>
</tr>
<tr>
<td>Monochorionic twins (4%)</td>
<td>Anemia and/or high-output cardiac failure</td>
<td>Twin-to-twin transfusion syndrome (usually the recipient but can occur in the donor), twin anemia polycythemia sequence Acardiac twin (donor)</td>
</tr>
<tr>
<td>Lymphatic dysplasia (15%)</td>
<td>Abnormal lymphatic drainage</td>
<td>Congenital lymphatic dysplasia</td>
</tr>
<tr>
<td>Neck/chest (2%)</td>
<td>Vena caval obstruction or increased intrathoracic pressure with impaired venous return</td>
<td>Cystic hygroma Congenital high airway obstruction Pleural effusion (chylothorax) Chest mass (congenital pulmonary airway malformation, sequestration, congenital diaphragmatic hernia)</td>
</tr>
<tr>
<td>Gastrointestinal (1%)</td>
<td>Obstruction of venous return, gastrointestinal obstruction and infarction with protein loss and decreased colloid osmotic pressure</td>
<td>Portal vein thrombosis Volvulus Obstruction Meconium peritonitis</td>
</tr>
<tr>
<td>Urinary tract (1%)</td>
<td>Urinary ascites; nephrotic syndrome with hypoproteinemia</td>
<td>Finnish nephrosis, urinary tract obstruction</td>
</tr>
<tr>
<td>Aneuploidy (13%)</td>
<td>Cardiac anomalies, lymphatic dysplasia, anemia, abnormal myelopoiesis</td>
<td>45,XO, trisomy 21, trisomy 18, triploidy</td>
</tr>
<tr>
<td>Hematologic (9%)</td>
<td>Anemia, high-output cardiac failure; hypoxia (α-thalassemia)</td>
<td>α-Thalassemia (homozygous) Fetomaternal transfusion</td>
</tr>
<tr>
<td>Infection (7%)</td>
<td>Anemia, anoxia, endothelial cell damage, increased capillary permeability, myocarditis</td>
<td>Parvovirus, cytomegalovirus, adenovirus, syphilis, toxoplasmosis</td>
</tr>
<tr>
<td>Inborn errors of metabolism (1%)</td>
<td>Anemia</td>
<td>Lysosomal storage disease, mucopolysaccharidoses, Gaucher disease, Niemann-Pick disease G6PD deficiency</td>
</tr>
<tr>
<td>Other syndromes (5.5%)</td>
<td>Visceromegaly, obstruction of venous return, decreased erythropoiesis, anemia, hypoproteinemia</td>
<td>Noonan syndrome Skeletal dysplasias such as achondroplasia, osteogenesis imperfecta, thanatophoric dysplasia arthrogryposis, congenital myotonic dystrophy</td>
</tr>
<tr>
<td>Extrathoracic tumors (1%)</td>
<td>Anemia, high-output cardiac failure, hypoproteinemia</td>
<td>Vascular/lymphatic tumors Teratoma, neuroblastoma, arteriovenous malformation</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td>Severe diabetes mellitus, severe anemia, severe hypoproteinemia, thyrotoxicosis Indomethacin use (premature closure of ductus arteriosus)</td>
</tr>
<tr>
<td>Placental/cord</td>
<td></td>
<td>Placental or umbilical vein thrombosis, cord knot, chorioangioma</td>
</tr>
</tbody>
</table>

*Adapted from references 4, 23, 36, 43, 226, and 230-237.
*Much higher percentage of hydrops in regions with α-thalassemia, such as Southeast Asia.
FIG. 41.2 Ascites. (A) Fluid outlines the liver. (B) Fluid outlines the bowel, compressing it posteriorly. (C) Ascites outlines the umbilical vein (arrow). (D) Fluid outlines the liver and stomach. Note associated skin thickening.

FIG. 41.3 Pseudoascites. (A) Transverse and (B) parasagittal ultrasound views show hypoechoic abdominal musculature and fat mimicking ascites. Note that this appearance will change with transducer angle, and the hypoechoic material will always be visualized in the subcutaneous regions, not surrounding bowel.
FIG. 41.4 Ascites. (A) Small amount of ascites (arrows). (B) Moderate amount of ascites. Note how the ascites surrounds loops of bowel. The bowel can appear echogenic because of through transmission from the fluid. See also Video 41.1.

FIG. 41.5 Hydrocele. Ultrasound of male fetus with hydrops with fluid extending into the scrotum.

chest mass such as a hernia or congenital pulmonary airway malformation (CPAM) should be sought (Fig. 41.7). Larger effusions will lead to flattening and eversion of the hemidiaphragms (Video 41.3) and, when sufficiently large, mediastinal shift. A large, unilateral effusion suggests a local cause, such as chylothorax. Although chylothorax begins as a unilateral effusion, it can progress to cause mediastinal shift, obstructing venous return and leading to hydrops. In large, bilateral pleural effusions the lungs appear as free-floating “bat wings” beside the heart (see Fig. 41.6D). When chronic, large effusions can lead to pulmonary hypoplasia. As pleural effusions enlarge, compression or kinking of mediastinal vascular structures causes upper body edema and functional esophageal obstruction, leading to secondary polyhydramnios.

Chylothorax is the most common cause of pleural effusion leading to respiratory distress in the newborn. This is an important diagnosis to suggest when associated with hydrops because drainage can be curative. Drainage of the effusion can lead to reversal of hydrops and can prevent pulmonary hypoplasia. Drainage immediately before delivery can assist in peripartum care. When drained, the fluid has a large number of lymphocytes in clear, yellow fluid. The fluid will not be “milky” until after the infant feeds.

In a recent review of 31 fetuses with primary hydrothorax, 24 had hydrops. Hydropic fetuses were more likely to present with bilateral effusions. Of all fetuses with primary hydrothorax, 21 had fetal interventions. Survival without hydrops was 7/7 (100%), whereas survival with hydrops depended on whether or not the patient had fetal intervention: 12/19 (63%) with intervention and 1/5 (20%) without intervention. Premature delivery was common (44%) among those who had fetal intervention.9

Pericardial Effusions

In contrast to pleural effusions that surround the lungs and compress the tissue medially, pericardial effusions are anteromedial fluid collections. Fluid collections of up to 2 mm in thickness are common, and a small amount of pericardial fluid (up to 7 mm, in isolation) can be a normal finding10 (Fig. 41.8, Video 41.4). A large pericardial effusion compresses the lungs against the posterior chest wall (Fig. 41.9). The heart is visualized as “floating” within the anterior thoracic fluid collection.
CHAPTER 41 Fetal Hydrops

FIG. 41.6 Fetal Pleural Effusions. (A) Unilateral small right pleural effusions. (B) Bilateral pleural effusions in fetus with abnormal heart and severe skin thickening. (C) Moderate right effusion. Note moderate mediastinal shift to the left. (D) Bilateral moderate effusions. Note how the partially compressed lungs appear as free-floating “bat wings.” (E) Axial and (F) oblique coronal views of large right pleural effusion. Note the severe mediastinal shift in E. See also Video 41.2.

FIG. 41.7 Small Pleural Effusion in Association With Congenital Pulmonary Airway Malformation. Note the large cystic mass (calipers) and small pleural effusion (arrow).

Subcutaneous Edema

Subcutaneous edema may be localized or generalized (Fig. 41.10), depending on the cause. A thickness of 5 mm has been suggested as the cutoff value. Edema is most easily seen over the fetal scalp or face, where thickening of skin overlying bone is visualized (Figs. 41.10A and 41.11A). It is important to realize that the biparietal diameter and head circumference measurements are taken around the skull bone, excluding the skin. Subcutaneous edema may also be seen over the limbs and abdominal wall. Care should be taken not to mistake prominent fat in a macrosomic fetus as anasarca in a hydropic fetus. Subcutaneous edema will increase the abdominal circumference measurement, beyond that which is expected for gestational age (Fig. 41.11B). It is important when measuring the fetus to include the entirety of the skin in the abdominal circumference measurement, because this affects the weight calculation of the fetus. Thus, when biometric assessment of the hydropic fetus is performed, the abdominal circumference measurement is included in the weight calculation, but it should be excluded from the gestational age assessment so that the thickened skin does not falsely elevate estimated fetal age. When generalized subcutaneous edema is present, the appearances may be referred to as “anasarca” (Fig. 41.12, Video 41.5).
Placentomegaly

Placental edema is a variable and usually late sign in hydrops (Fig. 41.13). The sonographic texture of the placenta may be altered, and its appearance may be described as thickened, echogenic, spongy, or ground glass. Placental dimensions, especially thickness, are increased above the normal of 4 cm thickness in the second trimester and 6 cm in the third trimester.\(^\text{11-15}\) When placental edema is secondary to a fetal abnormality, the entire placenta is usually affected. This finding may be used to exclude the very rare primary placental causes of hydrops (e.g., chorioangioma).

Polyhydramnios

The assessment of amniotic fluid is described in Chapters 39 and 42. Polyhydramnios occurs frequently in conjunction with hydrops (Fig. 41.14, see Video 41.1). A single amniotic fluid pocket of 8 cm or more, regardless of gestational age, is a useful threshold for polyhydramnios. Polyhydramnios increases the risk of prematurity, which adds to the morbidity associated with hydrops.

ETIOLOGY

Before the availability of Rho (D) immune globulin (RhoGAM), immune hydrops represented more than 80% of all cases of hydrops. Now, nonimmune hydrops represents more than 85% of cases. The distribution, timing, and size of fluid collections and edema as detected by ultrasound provide clues as to the etiology of hydrops. For example, in immune hydrops, ascites appears first, with subcutaneous edema appearing only with more advanced anemia. Intrathoracic collections generally do not occur or occur late in the process.

Generally, pleural and pericardial effusions appear earlier and more prominently with thoracic pathologies, whereas ascites appears earlier and predominates with anemia and primary abdominal pathologies. Massive ascites with associated bowel hyperechogenicity is typical of either parvovirus infection (when the ascites is very tense) or a bowel perforation that may be secondary to meconium peritonitis (Fig. 41.15). Localized fluid collections may progress to hydrops because of pressure or
metabolic effects, and thus the pattern of hydrops may evolve over time.

**IMMUNE HYDROPS**

Immune hydrops, or erythroblastosis fetalis, occurs when a sensitized mother develops antibodies to fetal RBCs that lead to hemolysis. Circulating maternal immunoglobulin G (IgG) antibodies cross the placenta and attack antigen-positive fetal RBCs. The majority of cases still occur in the presence of Rh(D) antibodies. Other antibodies such as Kell, Rh(C), and Rh(E) develop in 1% to 2% of individuals after blood transfusion and cause 2% of hemolytic disease of the fetus. The result is anemia, extramedullary erythropoiesis, hepatosplenomegaly, hypoalbuminemia, and congestive heart failure. Hydrops develops when the fetal hemoglobin (HbF) deficit exceeds 7 g/dL, probably because of reduced oncotic pressure secondary to hypoalbuminemia, combined with high-output cardiac failure. Eventually, the fetus develops both metabolic and lactic acidosis, and once this decompensation occurs, progression of hydrops is rapid, leading to fetal demise within 48 hours.

Causes of maternal sensitivity include fetal maternal hemorrhage and transplacental hemorrhage. In women with incompatible blood types with respect to the fetus (Rh alloimmunization or other RBC antigen), antibodies can be made. This typically occurs after delivery of the first pregnancy and therefore will affect the second pregnancy. Other times of blood sharing include miscarriage, therapeutic abortion, amniocentesis, placental
FIG. 41.12 Anasarca in Fetus With Turner Syndrome. (A) Axial view of cystic hygroma behind the neck. (B) Coronal view of diffuse scalp edema and cystic hygroma. (C) Axial view of thoracic wall edema. (D) and (E) Axial views of abdomen show body wall edema and ascites. (F) Arm with anasarca as well. See also Video 41.5 for example of anasarca associated with congenital pulmonary airway malformation.

FIG. 41.13 Placental Edema. Placental thickness is normally about 1 mm of thickness per week gestational age, and it should not exceed 5 cm in the third trimester.

FIG. 41.14 Polyhydramnios. A 12-cm pocket of fluid (cursors) in pregnancy complicated by fetus with hydrops.
abruption, incompatible blood transfusions, and transplacental hemorrhage. An additional blood incompatibility issue is fetal alloimmune thrombocytopenia.

To avoid maternal sensitization, 300 mg of RhoGAM is given at 28 weeks’ gestation in sensitized individuals. This protects against 30 mL of fetal blood. If a greater degree of fetomaternal hemorrhage is suspected, a Kleihauer-Betke test can be done to quantify fetal blood in maternal circulation to determine the necessary dose. As a prophylactic measure, RhoGAM is given to Rh-negative women within 48 hours after invasive fetal procedures such as amniocentesis and chorionic villus sampling.

Noninvasive Assessment of Alloimmunization

Fetuses are screened for risk of alloimmunization by determining the Rh status of the parents. If the pregnant woman is Rh negative, the father is screened. If the father of the baby is also Rh negative, no further screening is needed. If the mother is Rh negative and the father is Rh positive, maternal antibody titers are monitored. If they rise above 1:8, further testing is warranted. In the past, this was done with amniocentesis assessing for optical density (OD) of amniotic fluid (hemolysis increases OD of amniotic fluid), and serial percutaneous umbilical cord blood sampling (PUBS) procedures were performed as indicated to determine hematocrit (Hct). Currently, Hct is indirectly inferred from middle cerebral artery (MCA) Doppler studies, in which peak systolic velocity (PSV) is elevated in cases of anemia.

In response to severe anemia, the fetal circulation becomes hyperdynamic with increased blood flow velocities, which are thought to result from increased cardiac output and decreased viscosity of fetal blood. In addition, blood flow in the MCA may be increased further because the brain circulation responds quickly to hypoxemia. Although flow velocities in all fetal vessels will be increased, the MCA is particularly suitable for assessment because of its easy visualization with color Doppler imaging (Video 41.6) as it courses directly above the greater wing of the sphenoid bone, carrying more than 80% of cerebral blood flow. The MCA has a high-impedance circulation with continuous forward flow. The method for MCA Doppler includes finding the circle of Willis, measuring a pulsed Doppler waveform of the proximal MCA at the base of the brain soon after its origin from the internal carotid artery (ICA) and obtaining a PSV measurement with the angle of insonation close to 0 degrees (Fig. 41.16B). Intraobserver and interobserver variability is low. Technique is important for obtaining accurate results. In most cases the examination can be performed in less than 5 minutes.

<table>
<thead>
<tr>
<th>Measurement of Middle Cerebral Artery (MCA) Peak Systolic Velocity (PSV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Obtain an axial section of the head at the level of the sphenoid bones during a period of fetal rest.</td>
</tr>
<tr>
<td>2. Use color Doppler ultrasound to identify circle of Willis with MCA at angle close to 0 degrees.</td>
</tr>
<tr>
<td>3. Enlarge image of MCA such that it occupies more than 50% of the image.</td>
</tr>
<tr>
<td>4. Interrogate MCA soon after its origin from the ICA at angle close to 0 degrees using a 1- to 2-mm sample volume. (If an angle close to 0 degrees cannot be obtained, then angle correction can be utilized.)</td>
</tr>
<tr>
<td>5. Measure PSV.</td>
</tr>
<tr>
<td>6. Repeat the collection of MCA Doppler ultrasound three times.</td>
</tr>
<tr>
<td>7. Repeated waveforms should be similar.</td>
</tr>
</tbody>
</table>

The measured PSV is compared to median measures with respect to gestational age. A measurement of 1.5 multiples of the median (MoM) suggests severe anemia (Table 41.2). In a study of 111 fetuses at risk for anemia and 265 nonanemic fetuses, Mari et al. reported a sensitivity of a single value of MCA-PSV of nearly 100% for moderate or severe anemia with a false-positive rate of 12%.
FIG. 41.16 Middle Cerebral Artery (MCA) on Color Doppler Ultrasound. (A) Circle of Willis. (B) Spectral Doppler tracing. Note how Doppler gate is on the MCA just after the origin from the internal carotid artery. Note that the MCA is studied with an angle close to 0 degrees; therefore, the velocity is close to the real velocity of the blood flow. See also Video 41.6. (With permission from Mari G, Abuhamad AZ, Cosmi E, et al. Middle cerebral artery peak systolic velocity: technique and variability. J Ultrasound Med. 2005;24:425-430.)

### TABLE 41.2 Expected Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery as a Function of Gestational Age

<table>
<thead>
<tr>
<th>Week of Gestation</th>
<th>MULTIPLES OF THE MEDIAN (cm/sec)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1.00 (Median)</td>
</tr>
<tr>
<td>18</td>
<td>23.2</td>
</tr>
<tr>
<td>20</td>
<td>25.5</td>
</tr>
<tr>
<td>22</td>
<td>27.9</td>
</tr>
<tr>
<td>24</td>
<td>30.7</td>
</tr>
<tr>
<td>26</td>
<td>33.6</td>
</tr>
<tr>
<td>28</td>
<td>36.9</td>
</tr>
<tr>
<td>30</td>
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<td>32</td>
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<td>34</td>
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<td>36</td>
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</tr>
<tr>
<td>38</td>
<td>58.7</td>
</tr>
<tr>
<td>40</td>
<td>64.4</td>
</tr>
</tbody>
</table>


In 2009, Pretlove et al. published a meta-analysis (that included pooled data from nine studies) on the diagnostic value of MCA Doppler flow studies for fetal anemia. Severe anemia was detected with sensitivity and specificity of 75% and 91%, respectively. The use of the MCA-PSV trends (as opposed to a single measurement) may decrease the false-positive rate to less than 5%.

The timing of MCA-PSV examination surveillance depends on prior history, gestational age, and measured MCA-PSV MoM level. Surveillance should begin when the pregnancy is advanced enough such that a fetal blood sampling procedure or intrauterine transfusion can technically be completed, typically after 18 weeks of gestation. After 24 weeks of gestation, routine testing is usually done on a weekly basis but may be done more frequently with higher MoM levels or other abnormal ultrasound findings that are suggestive of developing anemia.

The middle cerebral artery peak systolic velocity (MCA-PSV) is increased in intrauterine growth-restricted fetuses, and therefore not all fetuses with elevated MCA-PSV will have anemia. A variable sign of anemia in the fetus is that of hepatosplenomegaly. The fetal liver and spleen increase in size because of their increased production of RBCs. However, the fetus may be able to compensate for the breakdown of RBCs and, in such cases, may have a large liver and spleen but would not necessarily be severely anemic. Conversely, more rapid breakdown of RBCs may prevent the fetus from adapting to hemolysis. Therefore, anemia may develop without hepatosplenomegaly.

MCA Doppler ultrasound can help time a second fetal transfusion procedure, but need for subsequent transfusions are better predicted by estimating the decrease in fetal hematocrit over time.

Immune hydrops is an indication for urgent fetal blood sampling and transfusion. Use of MCA-PSV data allows for PUBS procedures to be timed to the need for in utero transfusions. In a study of 80 fetuses with hydrops secondary to anemia, when hydrops was mild before treatment (only a thin rim of ascites, with or without pericardial effusion), hydrops was reversed in 88%; when hydrops was severe before treatment, hydrops reversed in only 65%. This stresses the importance of early treatment in cases of suspected anemia. After reversal of hydrops, survival rate was 98%.

It should be recognized that immune hydrops, even untreated, is not uniformly lethal, and can spontaneous reverse, particularly if hydrops is mild, and an infection, such as parvovirus, is self-limited. Complications of transfusion for fetal anemia are detailed.

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It should be recognized that immune hydrops, even untreated, is not uniformly lethal, and can spontaneous reverse, particularly if hydrops is mild, and an infection, such as parvovirus, is self-limited. Complications of transfusion for fetal anemia are detailed.
Nonimmune hydrops occurs in 1 in 1500 to 1 in 4000 pregnancies. It is a common pathologic finding in first- and second-trimester spontaneous abortions. The cause varies geographically and with gestational age. In North America and Europe, most cases are cardiovascular (20%), hematologic (9%), infective (7%), or chromosomal (13%; usually Turner syndrome; trisomy 21 and 18) in origin (see Table 41.1). In Southeast Asia, however, homozygous α-thalassemia is a common cause; in this region, carrier status for α-thalassemia occurs in 5% to 15% of the population. Nonimmune hydrops in homozygous α-thalassemia accounts for 25% of perinatal deaths in Southeast Asia.

Pathophysiology

Nonimmune hydrops represents the terminal stage for many conditions and is frequently multifactorial. Pathophysiology of hydrops may involve increased hydrostatic pressure, high-output cardiac failure, decreased plasma oncotic pressure, increased capillary permeability, obstruction of lymph flow, or a combination of these factors (Fig. 41.17). Fluid collections result from redistribution of fetal body fluids among the intravascular, intracellular, and interstitial compartments, secondary to an imbalance in capillary ultrafiltration and interstitial fluid return. Hypoxia and circulatory failure may result in capillary damage that leads to plasma protein and fluid loss from the intravascular compartment.

Several factors predispose to edema in the fetus versus after birth. Both total body and extracellular fluid compartments are proportionately greater in the fetus, particularly at earlier gestational ages. Colloid osmotic pressure is lower because of lower albumin concentrations. High compliance of the interstitial space facilitates the accumulation of large volumes of fluid. Many causes of hydrops, especially those with a cardiac component, result from an increase in systemic venous pressure, to which the fetus is particularly sensitive. In the fetus, there is a net movement of fluid from the intravascular to the extracellular space. Fivefold larger volumes of fluid are removed by the lymphatics in fetal models than in adult animal models. Thus small elevations in systemic venous pressure (2-3 mm Hg) in the fetus can substantially reduce lymphatic flow and can drive large amounts of fluid into the extracellular space. This process is further enhanced by the relatively greater permeability of fetal capillaries to protein. The fetus is therefore particularly susceptible to small elevations in venous pressure from a number of causes, all of which can result in hydrops.

Causes and Associations

Nonimmune hydrops most commonly has a fetal etiology but also may be caused by maternal or placental factors. Maternal causes (such as poorly controlled diabetes mellitus) are rare and should be differentiated from maternal complications, which are secondary to fetal hydrops (termed mirror syndrome because edema develops in the mother of an hydropic fetus, “mirroring” the condition in the fetus). Maternal thyrotoxicosis can cause fetal hyperthyroidism and fetal hydrops, with potential for resolution of hydrops after treatment with antithyroid drugs. Placental causes, such as chorioangioma and other vascular shunts, are relatively rare and are usually associated with high-output failure states and, in some cases, fetal anemia. Chorioangiomas need to be large (>4.5 cm) before they lead to hemodynamic compromise. They can be treated by laser, radiofrequency ablation, and/or surgical clip application. Fetal metabolic causes are rare but important, because diagnosis can lead to appropriate neonatal treatment and appropriate counseling of the patients regarding recurrence risks.

A classification scheme for fetal causes is shown in Table 41.1 and has some overlap in the groupings, some of which represent associations rather than causations.

Cardiovascular Abnormalities

Structural cardiovascular abnormalities (Fig. 41.18) are the cause of hydrops in about 20% of cases. However, hydrops is a rare complication of isolated cardiac abnormality because the fetus has a parallel flow circulation. In chromosomal abnormalities, for example, other factors with or without cardiac abnormality lead to hydrops.

Right-sided lesions, whether obstructive, such as pulmonary or tricuspid atresia, or structural lesions that result in right atrial volume or pressure overload, such as mitral regurgitation, can result in congestive heart failure and hydrops. Left-sided obstructive lesions, such as aortic stenosis, mitral stenosis, and coarctation of the aorta, can result in a hypoplastic left heart, causing increased blood flow through the fetal right ventricle, which may result in hydrops. The prognosis of nonimmune hydrops fetalis caused by cardiac structural abnormalities is poor, with a combined fetal and infant mortality rate of 92%, largely because of the severity of the heart defects that cause in utero congestive heart failure. Some fetuses with structural cardiac anomalies also have rhythm disturbances, which contribute to the poor prognosis. In a series of 301 fetuses with atrioventricular
(AV) septal defects, the presence of fetal hydrops, together with bradycardia from sinus node dysfunction or complete heart block, was associated with a poor outcome.\(^{44}\)

**Cardiac Tumors.** Cardiac tumors are a rare cause of hydrops.\(^{45-50}\) Hydrops in the context of cardiac tumors may be caused by several mechanisms, depending on the tumor location, size, and number. Cardiac lesions may cause obstruction to blood flow and alteration of AV valve function and may lead to arrhythmia, cardiac tamponade, pericardial effusion, and hydrops.\(^{47-49}\)

Rhabdomyomas are the most common fetal cardiac tumor and are seen in association with tuberous sclerosis in more than 80% of cases.\(^{50}\) Rhabdomyomas are also the most common cardiac tumors to cause hydrops. Usually, these tumors are multiple, well-circumscribed, hyperechoic, and homogeneous and mainly involve the ventricular myocardium\(^ {48}\) (Fig. 41.19). Rhabdomyomas tend to grow during the second half of pregnancy,\(^ {25}\) so most are diagnosed during the second and third trimesters.

**Intrapericardial teratomas** are rare, usually appearing as cystic and solid masses outside the cardiac cavities, arising from the pericardium. Teratomas may be larger than the heart, and rapid growth of the tumor within the small, confined space can result in pericardial effusion and hydrops as a result of cardiac compression.\(^ {52,53}\) Drainage of pericardial fluid associated with an intrapericardial teratoma has been reported, with resolution of associated hydrops.\(^ {54,56}\) Frequently, more than one drainage procedure is necessary.\(^ {56}\) At times, a shunt is placed if fluid rapidly reaccumulates after drainage.\(^ {57}\) Drainage of pericardial effusion secondary to intrapericardial teratoma usually results in a live birth after 32 weeks’ gestational age.

**Arrhythmias.** Arrhythmias associated with hydrops are most often tachyarrhythmias (≥200 beats/min) and, less frequently, bradyarrhythmias. The diagnosis is important because treatment can reverse the hydrops. It is important to avoid premature delivery; treatment of a hydropic preterm fetus is difficult. Fetal tachyarrhythmias are most often supraventricular tachycardia (SVT, which includes atrial fibrillation/flutter)\(^ {58}\) (Fig. 41.20). The prognosis for a fetus with an isolated arrhythmia is favorable, with a 95% likelihood of survival.\(^ {59}\) However, when hydrops is present (41% in this series) with an otherwise isolated arrhythmia, the survival decreases to 73%.\(^ {58}\) When studying neonates who had fetal SVT, most cases are the result of reentry circuits.\(^ {60}\) If the SVT is of limited duration, there are typically no fetal consequences. However, with sustained SVT, hydrops may develop. The presence of hydrops in these cases is associated with more difficult prenatal antiarrhythmic control of the tachycardia and higher mortality. Prenatal control of the tachycardia was achieved in 83% of treated nonhydropic fetuses, compared with 66% of the treated hydropic fetuses.\(^ {58}\)

Tachyarrhythmia treatment is almost always given transplacentally; the pregnant woman is given an antiarrhythmic drug, which crosses the placenta and enters the fetal circulation. Rarely is direct fetal administration required.\(^ {31}\) At present, there is no consensus on first-line treatment of SVT. In one report flecainide and digoxin were slightly more effective than sotalol.\(^ {61}\) Combination therapies (amiodarone/digoxin, amiodarone/flecainide, sotalol/digoxin, and sotalol/flecainide) have been reported to be effective when single agents have failed.\(^ {62}\) Treatment for SVT has been described as early as 13 weeks’ gestational age.\(^ {63}\) Prognosis in the setting of fetal tachyarrhythmia depends on a number of factors, including type and duration of arrhythmia, presence of structural cardiac anomalies, gestational age, and response to intrauterine therapy.\(^ {64}\)

In rare cases of SVT and hydrops, preterm delivery (if at sufficient gestational age) may be the best option, allowing for direct treatment of the tachyarrhythmia. Again, however, treatment of a hydropic preterm infant is difficult, and therefore preterm delivery is usually not indicated.
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Heart Block. Congenital heart block (CHB) is a rare cardiac conduction defect, occurring in 1 in 15,000 to 1 in 20,000 live births. In fetuses with CHB, hydrops results from a combination of low cardiac output, a slow heart rate, and a structural lesion, if present. The increased venous pressure in association with low colloid oncotic pressure leads to edema. Because approximately one-third of fetuses with CHB have associated structural heart defects, a detailed fetal echocardiographic assessment is always warranted.

In isolated heart block, maternal rheumatologic disease is common. Maternal serologic testing for anti-Ro/La antibodies is warranted because transplacental passage of maternal anti-Ro and anti-La autoantibodies is seen in 95% of cases of fetal CHB. These antibodies cross the placenta from as early as 16 weeks' gestational age and initiate inflammatory damage to the fetal conduction system and myocardium. Hydrops develops with ventricular rates less than 60 beats/min (about 40% of cases with isolated heart block) and has a mortality rate of 25% to 100%. Treatment can be given with steroids and plasmapheresis, but the efficacy of these is not well established. Epicardial pacemaker can be placed at birth. Although 95% of mothers tested positive for anti-Ro/La antibodies, fewer than 5% of these pregnant patients had signs and symptoms of connective tissue disease at diagnosis of fetal AV block.

When structural abnormalities accompany heart block, hydropic fetuses have a combined fetal and neonatal mortality rate of 83% to 100%. Jaeggi et al. reported 29 cases of prenatally diagnosed isolated congenital AV block; six fetuses presented with hydrops; two died antenatally, and four died in the neonatal period. In these cases, corticosteroid use during pregnancy did not reverse hydrops or reduce the severity of AV block. In addition to hydrops, other poor prognostic factors include endocardial fibroelastosis with ventricular dysfunction and coexistent structural heart disease.

Decreased Myocardial Function. Cardiomyopathies can be classified as primary or secondary or by an echocardiographic evaluation as dilated or hypertrophic. Primary fetal cardiomyopathies may have intrinsic causes (e.g., single-gene disorders, mitochondrial disorders, chromosomal abnormalities, α-thalassemia) or extrinsic causes such as infection, maternal disease (autoantibodies or insulin-dependent diabetes), and twin-twin transfusion syndrome. Secondary fetal cardiomyopathies are associated with structural or functional cardiac disorders (Video 41.7) and high-output states.

Neck Abnormalities

Neck masses, such as teratomas and lymphangiomas, cause fetal hydrops from compression or high-output cardiac failure (Fig. 41.21). A cystic hygroma (fluid in posterior neck) may indicate a chromosomal (e.g., 45,XO) or other abnormality. Of 42 fetuses with first-trimester cystic hygroma, 14 developed hydrops later in pregnancy. Each of these had a nuchal translucency measurement of 3 mm or more at diagnosis of cystic hygroma. For fetuses presenting with hydrops in the first trimester, all have increased nuchal translucency.

Thoracic Anomalies

Hydrops can result from obstruction of venous or lymphatic return due to maldevelopment, compression, kinking, or cardiac tamponade. Mediastinal masses, pleural effusions, and diaphragmatic hernias may cause nonimmune hydrops by similar mechanisms.

The incidence of fetal hydrothorax is estimated at 1 in 15,000 pregnancies. Isolated hydrothorax is most often caused
Obstetric and Fetal Sonography

PART IV

When a fetus with CPAM develops hydrops, the prognosis is poor, and antenatal intervention is often advisable. Intervention may be in the form of decompression by cyst aspiration (see Fig. 41.22), shunt, or open fetal surgery. A 2006 meta-analysis showed that shunting of CPAMs improved survival in fetuses with hydrops, as opposed to no effect on survival in fetuses with chest masses without hydrops.

Antenatal predictors of progression to hydrops include a combination of microcystic and macrocystic components and a large volume ratio of the mass to the normal lung (>1.6). For fetuses with no dominant cyst and CPAM volume ratio less than 1.6, 97% did not progress to hydrops, whereas in the group with volume ratio greater than 1.6, 75% progressed to hydrops. The success with open fetal surgery in cases of CPAM is variable, 29% to 62%. Antenatal aspiration of a macrocystic CCAM at times may be an effective treatment, but frequently it is ineffective because of rapid reaccumulation of the cyst fluid. In cases with rapid reaccumulation of fluid, thoracoamniotic shunting may be a better approach.

Survival after shunting is correlated to gestational age at birth, percent reduction in lesion size, and resolution of hydrops. Maternal administration of steroids also may be helpful. Although nonimmune hydrops fetalis rarely occurs in BPS cases, it is associated with a high rate of perinatal mortality and severe respiratory insufficiency in the neonate. However, neonates with BPS and hydrops can survive.

In a report of 67 cases of lung masses, only 7% developed hydrops. Of 134 fetuses with CPAM referred to two fetal surgical centers in the United States, 101 were followed expectantly, and all 25 hydropic fetuses died, whereas all 76 nonhydropic fetuses survived, suggesting that fetal surgery might be considered for hydropic cases. In the absence of hydrops, and provided there are no other anomalies, survival in these cases is virtually 100%.

When a fetus with CPAM develops hydrops, the prognosis is poor, and antenatal intervention is often advisable. Intervention may be in the form of decompression by cyst aspiration (see Fig. 41.22), shunt, or open fetal surgery. A 2006 meta-analysis showed that shunting of CPAMs improved survival in fetuses with hydrops, as opposed to no effect on survival in fetuses with chest masses without hydrops. Antenatal predictors of progression to hydrops include a combination of microcystic and macrocystic components and a large volume ratio of the mass to the normal lung (>1.6). For fetuses with no dominant cyst and CPAM volume ratio less than 1.6, 97% did not progress to hydrops, whereas in the group with volume ratio greater than 1.6, 75% progressed to hydrops. The success with open fetal surgery in cases of CPAM is variable, 29% to 62%. Antenatal aspiration of a macrocystic CCAM at times may be an effective treatment, but frequently it is ineffective because of rapid reaccumulation of the cyst fluid. In cases with rapid reaccumulation of fluid, thoracoamniotic shunting may be a better approach. Survival after shunting is correlated to gestational age at birth, percent reduction in lesion size, and resolution of hydrops. Maternal administration of steroids also may be helpful.

Although nonimmune hydrops fetalis rarely occurs in BPS cases, it is associated with a high rate of perinatal mortality and severe respiratory insufficiency in the neonate. However, neonates with BPS and hydrops can survive. Different strategies of in utero treatment have been proposed, such as thoracoamniotic shunting of pleural effusion, thoracentesis and intravascular furosemide and digoxin, alcohol ablation of the vascular pedicle with placement of a shunt, ablation of the abnormal systemic artery from the aorta, and open fetal surgery.

In CHAOS the mechanism of hydrops is secondary to cardiac and great vessel compression by the enlarged fetal lungs.

**Chest Drainage Procedures.** Aneuploidy is present in about 6% of cases of chylothorax and should be excluded.
Shunt placement resulted in a 55% ± 21% decrease in macrocystic lung lesion volume and complete or partial drainage of the pleural effusion in 29% and 71% of fetuses. Sixty-nine percent of fetuses presented with hydrops, which resolved following shunt placement in 83%. Survival was 68%, which correlated with gestational age at birth, percent reduction in lesion size, unilateral pleural effusions, and hydrops resolution.

Gastrointestinal Anomalies
Anomalies of the gastrointestinal tract typically cause isolated ascites rather than hydrops. If there is local obstruction of lymphatic and venous drainage, as from intestinal obstruction, volvulus, or omphalocele, hydrops may result in rare cases. Abdominal masses presumably act by compression of venous

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**FIG. 41.22** Drainaging of macrocystic congenital pulmonary airway malformation with mediastinal shift and incipient hydrops. (A) shows a cyst in the cyst (c) with mediastinal shift of the heart (H). (B) shows needle in the largest cyst. (C) shows decreased size of the cyst. Needle can be seen (arrows). (D) At the completion of the procedure, the heart (H) is less compressed, and the echogenic chest mass (c) can still be seen, but the large cyst is no longer present.
Urinary tract anomalies are rare causes of hydrops. Congenital nephrosis can lead to severe proteinuria and hypoalbuminemia as the cause of hydrops.

Bladder rupture can lead to urinary ascites but rarely hydrops (Fig. 41.24).

Lymphatic Dysplasia

Congenital lymphatic dysplasia may be the source of many cases of hydrops that do not have an obvious cause. Bellini et al. found that six newborns presenting at birth with hydrops of unidentified cause all had lymphatic dysplasia.
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Monochorionic Twins

Twins have an increased incidence of hydrops secondary to a higher incidence of congenital anomalies and secondary to complications associated with the monochorionic placenta: twin-twin transfusion syndrome (TTTS) and acardiac twinning. These are described in detail in Chapter 32. The Quintero classification of TTTS has, as stage IV, hydrops of one or both twins. The recipient twin experiences an elevation in cardiac output and blood pressure as a result of shunting of blood through the AV anastomoses. Initially, the increase in right ventricular workload is compensated for by ventricular hypertrophy, with minimal hemodynamic dysfunction. With ongoing volume and pressure overload, the right ventricle stretches and the tricuspid regurgitation begins, probably associated with increase in right ventricular end-diastolic pressure, reflected in the end-diastolic pressure of the right atrium. Atrial contractions against an elevated pressure produce retrograde flow during atrial systole in the ductus venosus, hepatic veins, and inferior vena cava. Eventually, metabolic acidosis and congestive heart failure develop. Conservatory management of early-onset severe TTTS is associated with a survival rate of less than 10%. Death is caused by extreme prematurity, in association with growth restriction in the donor and cardiac failure and hydrops in the recipient (Fig. 41.25). Current series suggest improved survival and decreased neurologic sequelae if severe TTTS before 26 weeks is treated with endoscopic selective laser ablation of the placental vascular anastomoses.

For this procedure, a laser is introduced endoscopically into the uterus and used to ablate surface placental vessel anastomoses under ultrasound guidance.

In acardiac twins (twin reversed arterial perfusion [TRAP] sequence) a monochorionic pair has a pump twin and an acardiac twin. The pump twin perfuses the acardiac twin and develops high-output cardiac failure (particularly if the weight of the acardiac twin is >70% of the donor twin) and polyhydramnios. The acardiac twin has anasarca but not true hydrops. Treatment involves interruption of the blood flow to the acardiac twin, typically by radiofrequency ablation, laser ablation, or cord ligation. Radiofrequency ablation can result in survival of 80%.

Chromosomal Anomalies

The incidence of aneuploidy is higher in hydrops cases presenting before 24 weeks than those later in pregnancy. Before 24 weeks, the incidence of aneuploidy in cases of hydrops ranges from 33% to 78%. After 24 weeks the incidence of aneuploidy in hydrops is as low as 2%.

Turner syndrome (45,XO) is classically associated with a cystic hygroma in the first and early second trimesters (Fig. 41.26; see also Fig. 41.12). Many of these disorders result in early spontaneous abortion. Trisomies 21, 18, and 13 and triploidy have been associated with nonimmune hydrops, although it is

FIG. 41.24 Lower Urinary Tract Obstruction. Urinary ascites in obstructive uropathy with bladder rupture. Note the thickened bladder wall.

FIG. 41.25 Twin-Twin Transfusion Syndrome at 20 Weeks’ Gestation. (A) Polyhydramnios and hydropic recipient twin. (B) Note membrane (arrow) closely adjacent to the stuck (donor) twin.
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PART IV

Tumors

Arteriovenous malformations and arteriovenous shunting in large tumors with a high proportion of solid tissue lead to hydrops by causing high-output cardiac failure and leading to Kasabach-Merritt sequence (consumptive coagulopathy). Selected fetuses with tumors, such as large sacrococcygeal teratoma associated with hydrops, have undergone in utero procedures, including cyst aspiration and open fetal surgical resection. However, these procedures are complicated by preterm delivery and other obstetric complications. More recent reports suggest improved outcomes with laser ablation or alcohol sclerosis targeting the

often unclear why hydrops develops. There are a few reports of transient abnormal myelopoiesis with trisomy 21 as a cause of hepatomegaly and nonimmune hydrops. In these cases, PUBS demonstrates fetal anemia and hypoalbuminemia. A hydropic fetus with multiple structural anomalies, prominent cystic hygromas, or increased nuchal translucency likely has a chromosomal abnormality. The physiologic basis for increased nuchal translucency is incompletely understood, but it may be caused by delayed lymphatic development and/or related to cardiovascular malformations, especially in cases with aneuploidy.

FIG. 41.26 Turner Syndrome in First and Second Trimesters. (A) Fetus at 12 weeks with diffuse skin thickening and lymphangiectasia. (B) and (C) Fetus at 13 weeks with nuchal thickening and diffuse body wall edema. (D)-(G) Fetus at 18 weeks with cystic hygroma and pleural effusion and diffuse body wall edema. (H) and (I) Fetus at 19 weeks with cystic hygroma (arrow) and ascites (A).
feeding vessel(s) of the tumor. In utero treatment for sacrococcygeal teratoma has a survival rate of 30% to 55%.143

Anemia

Fetal anemia is caused by decreased RBC production, increased hemolysis, or hemorrhage. If the process is gradual, the fetus mounts a compensatory erythropoietic response, and nonimmune hydrops develops only when the anemia exceeds its ability to keep pace, which is typically when the hemoglobin concentration deficit is 7 g/dL or greater.17 Hydrops results from a combination of high-output cardiac failure and hypoxic capillary damage, causing protein leakage, as well as infiltration of the liver by erythropoietic tissue, leading to portal hypertension.17

Decreased Red Blood Cell Production. Homozygotes with α-thalassemia cannot manufacture HbF in utero or hemoglobin A (HbA) after birth.144 Instead, Hb Bart is formed in utero, which has such a high affinity for oxygen that tissue hypoxia results, leading to capillary damage, protein leakage, cardiac failure, and hydrops. Other causes of decreased RBC production in utero include generalized marrow aplasia, as found in parvovirus infection32,145 and fetal leukemia.138

Hemolysis. Glucose-6-phosphate dehydrogenase (G6PD) deficiency has been reported as a rare cause of nonimmune hydrops resulting from increased hemolysis.146 Hemolysis may also contribute to anemia caused by in utero infection.

Hemorrhage. Blood loss may occur either into another fetus in TTTS, into the fetus itself (e.g., intracranial), into a tumor (e.g., sacrococcygeal teratoma), or transplacental.

Infection

Intrauterine infections account for up to 16% of cases of nonimmune hydrops.147 An autopsy series of fetuses with in utero demise and nonimmune hydrops showed that 33% had infection.148 Hydrops may result from effects on the bone marrow (parvovirus, cytomegalovirus [CMV], toxoplasmosis), myocardium (adenovirus, coxsackievirus, CMV, leading to congestive heart failure), vascular endothelium (hypoxic capillary damage causing protein leakage), or overwhelming sepsis with hepatitis and decreased protein production (syphilis).149-154 In addition to hydrops, signs of infection include calcifications in the pericardium or brain, as well as ventriculomegaly.

Parvovirus B19. Parvovirus B19 is responsible for up to 27% of cases of nonimmune hydrops.155 Myocarditis and fetal anemia secondary to bone marrow aplasia are thought to be the mechanisms of hydrops (Fig. 41.27). The marrow is particularly sensitive to parvovirus infection from 16 to 24 weeks’ gestation.149 The impact on RBC aplasia is further pronounced by the shortened life span of RBCs (45-70 days).156

Fetal infection occurs in up to 10% of pregnancies with maternal infection. This leads to an excess fetal loss rate of 9% of fetuses infected between 9 and 20 weeks’ gestation.157 In the first trimester, fetal infection can cause miscarriage, whereas in the second trimester, the fetus is at risk for hydrops. In contrast to most other congenital infections, adverse long-term sequelae are rarely associated with parvovirus.152 Although hydrops associated with parvovirus B19 can spontaneously resolve without transfusion,158-161 most cases benefit from intrauterine transfusion. Parvovirus infection is suspected when maternal blood shows positive immunoglobulin M (IgM, indicating a recent infection) and high or increasing IgG. Cordocentesis will show aplastic anemia with few reticulocytes, although at times the hydrops is caused by myocarditis.158 Fetal parvovirus infection is diagnosed by polymerase chain reaction (PCR) testing of amniotic fluid or fetal blood.162 PCR results can be available within a few hours. When maternal parvovirus infection is discovered, serial monitoring of the pregnancy is indicated, with weekly sonograms

*FIG. 41.27* Hydrops in Fetus With Parvovirus Infection and Anemia at 19 Weeks. (A) Transverse view of the fetal thorax shows a slightly enlarged heart with echogenic myocardium and small pericardial effusion. (B) Transverse view of abdomen shows ascites. Middle cerebral artery Doppler studies (not shown) showed peak systolic velocity of 55 cm/sec, indicating severe anemia.
for 8 to 12 weeks after maternal infection. Sonograms are performed to assess for signs of hydrops and include Doppler analysis to assess for elevated MCA velocity, as an indication of fetal anemia.

In cases of infection with parvovirus treated with intrauterine transfusion, survival is 43% to 84%. However, there are also reports of abnormal developmental outcome in up to 31% of cases.

Toxoplasmosis. Congenital infection with Toxoplasma gondii can cause anemia, intracerebral or intrahepatic calcifications, ventriculomegaly, and chorioretinitis and can present with hydrops, particularly ascites. Most pregnant women with congenital toxoplasmosis are asymptomatic or only mildly symptomatic during pregnancy. The rate of fetal infection varies according to the gestational age at the time of vertical transmission, ranging from 26% to 40%. Prenatal diagnosis of toxoplasmosis can be difficult and depends on the demonstration of maternal seroconversion and/or the parasite in amniotic fluid by PCR or isolation techniques. Diagnosis is important because infected mothers are treated with spiramycin throughout pregnancy. If fetal infection was demonstrated, pyrimethamine and sulfadiazine are added to the regimen.

Other Infections. Congenital CMV infection is responsible for 1% to 2% of cases of nonimmune hydrops and can occur even with recurrent maternal infection. Fetal treatment can be attempted with umbilical vein injection of ganciclovir or intraperitoneal injection of hyperimmunoglobulin. Rubella, syphilis, and varicella are less common causes of nonimmune hydrops. Diagnosis is important; in cases of syphilis, if the fetus is in the third trimester and the lungs are mature, delivery and treatment with penicillin can lead to resolution of the hydrops. Rare infectious causes of nonimmune hydrops include herpes simplex virus, adenovirus, and acute maternal hepatitis B infection.

Genetic Disorders
Multiple nonchromosomal genetic conditions can cause nonimmune hydrops (see Table 41.1). The mechanisms are poorly understood and are multifactorial. In storage diseases, the most likely mechanism is hepatic infiltration resulting in hypoproteinemia or vascular obstruction.

Metabolic Disorders
Inborn errors of metabolism are rare, and these are a rare cause of hydrops. However, diagnosis is important because early treatment of some disorders can lead to improved outcome. Diagnosis is also important for genetic counseling regarding recurrence risk. Lysosomal disorders associated with hydrops fetalis include GM1 gangliosidosis, galactosialidosis, infantile free–sialic acid storage disease, mucopolysaccharidosis types IV and VII, mucolipidosis types I and II, Gaucher disease type II, Faber disease, Niemann-Pick disease, Wolman disease, and multiple sulfatase deficiency. Hydrops fetalis has been associated with deficiencies of G6PD or pyruvate kinase. Pearson syndrome and other mitochondrial disorders congenital defects of N-glycosylation, glycogen storage disease type IV, and neonatal hemochromatosis.

Skeletal Disorders
Skeletal dysplasia is a rare cause of hydrops. Examples include achondroplasia, achondrogenesis, osteogenesis imperfecta, hypophosphatasia, and arthrogryposis.

Endocrine Disorders
Fetal endocrine disorders are rare causes of nonimmune hydrops. Fetal hypothyroidism and hyperthyroidism can cause hydrops. Hydrops can develop from maternal antibodies crossing the placenta, even if the pregnant patient has already been treated for Graves disease.

Drugs
In utero exposure to indomethacin can result in ductus arteriosus constriction and, rarely, hydrops. Because of this, ultrasound evaluation of the ductus arteriosus should be performed within 48 hours of starting indomethacin therapy.

Idiopathic Disorders
The number of idiopathic cases of nonimmune hydrops (for which we still cannot identify a cause) is about 10%, and will continue to decrease as our investigative abilities improve.

Systematic prenatal evaluation can establish a cause for nonimmune hydrops in up to 90% of cases. This is important not only for the management of the current pregnancy but also for future genetic counseling. A detailed history may provide the first clues to the cause and may suggest appropriate investigations. For example, a maternal history of systemic lupus erythematosus or diabetes may be relevant, and homozygous α-thalassemia is particularly prevalent in patients of Southeast Asian origin. Blood type can supply a clue to isoimmunization. Maternal diseases with anemia or infection are important. Previous pregnancy losses may be related to one of the inborn errors of metabolism or chromosome rearrangements, and the family history or presence of consanguinity may suggest other genetic conditions. Parvovirus infection is more likely to occur in teachers or day-care workers. Medication use can at times establish a cause.

Complete Obstetric Ultrasound
A comprehensive sonographic evaluation should be the initial step. However, no cause is found through use of sonography in 15% to 30% of cases. Polyhydramnios is a common association. A common indication for ultrasound is the clinical suspicion of being large for gestational dates. Collections of fluid in the pleural, peritoneal, and pericardial spaces are diagnostic, and their relative distribution and the timing of their development may give a clue to the cause. Ultrasound markers of aneuploidy suggest
TABLE 41.3  Workup of Hydrops After Fetal Echocardiogram, Maternal History Including Family History, Medications, Exposures

<table>
<thead>
<tr>
<th>Anatomic Survey</th>
<th>Maternal Tests</th>
<th>Additional Fetal Tests</th>
<th>Invasive Tests/Treatment</th>
<th>Tests of Amniotic Fluid/Fetal Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structurally normal</td>
<td>Blood type Rh(D) antigen status Indirect Coombs test (antibody screen) Kleihauer-Betke test Parvovirus serology (other infections to consider: syphilis, CMV, toxoplasmosis) Check Ro/La if bradycardia</td>
<td>MCA Doppler</td>
<td>Treat if tachyarrhythmia Amniocentesis</td>
<td>Karyotype and/or chromosomal microarray; PCR for CMV and toxo AFAFP Lysozyme enzyme testing Karyotype and/or chromosomal microarray PCR for CMV and toxo and parvovirus Consider G6PD, pyruvate kinase deficiency, lysosomal enzyme testing if no other cause</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td></td>
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<td></td>
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<tr>
<td>No arrhythmia, MCA Doppler normal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anemia (MCA-PSV &gt; 1.5 MoM)</td>
<td>MCV of parents to check for thalassemia (&lt;80 suggests carrier status)</td>
<td>Amnio (at time of PUBS), transfuse if needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structurally abnormal</td>
<td></td>
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A systematic detailed survey of fetal anatomy should be performed, searching for other clues to the cause of the hydrops. The fetal bladder should be visualized to exclude urinary ascites caused by bladder rupture. Bone length, curvature, density, and presence or absence of fractures should be evaluated to exclude skeletal dysplasias. Stigmata of congenital infection should be assessed, such as microcephaly or calcifications within the fetal brain or liver. A dedicated fetal echocardiographic structural and functional assessment is warranted to evaluate fetal heart structure, rhythm, and function in hydrops.

Maternal Investigations

Maternal blood type, indirect Coombs test (antiglobulin titer), and presence or absence of RBC antibodies should be checked to exclude immune hydrops. Other baseline tests include a complete blood count (CBC) and indices, Kleihauer-Betke test, infection screen (TORCH, parvovirus IgM/IgG), and glucose.

Fetal Investigations

Amniocentesis for fetal karyotype (if at an appropriate gestational age), antigen tests by PCR, and culture for syphilis, CMV, and toxoplasmosis are often indicated. MCA Doppler should be performed, with PUBS when the Doppler indicates anemia. Fluid aspirated from one of the fetal body cavities can also be used for fetal testing. The most appropriate choice depends on gestational age, accessibility, and urgency of results. A rapid karyotype can be obtained successfully from most collections of fetal body fluid. Fluorescent in situ hybridization (FISH) can be used to identify common aneuploidies (trisomies 13, 18, and 21; monosomy X or Turner syndrome) and other specific deletions and chromosome rearrangements. This technique can provide a result from amniotic fluid in 24 to 48 hours. In practice, the
confirmation or exclusion of the most common aneuploidies is often adequate to guide pregnancy management. Amniotic fluid is preferable for both viral culture and PCR for toxoplasmosis and CMV, and it can be used to assess fetal lung maturity at later gestations. Chorionic villous sampling is an alternative at any gestation for obtaining a rapid karyotype or DNA testing.

Fetal blood sampling is a key investigation in many cases when the chromosomes do not provide a diagnosis. Basic fetal blood work should include a direct Coombs test, CBC and indices, karyotype, protein, albumin, and viral-specific IgM. Other tests are done selectively, and samples can be stored for subsequent evaluation. With this approach, the cause of hydrops can be determined in most cases.

**Performing PUBS**

Cordocentesis has a 1% to 1.6% risk of fetal loss. The fetal risks need to be interpreted knowing that these fetuses are at particularly high background risk for fetal loss and adverse outcomes. Ghidini et al. performed a meta-analysis that excluded cases with pathologic fetal conditions and determined that the loss rate in a “low-risk” population undergoing fetal blood sampling was approximately 1.4%. A more recent study found that procedure-related complications of 3.1% and procedure-related loss rates of 1.6%. Other complications of cordocentesis include fetal bradycardia (4%-12%), bleeding at puncture site (20%-40%), hematomas (17%), infection (1%), abruptio (rare), fetomaternal hemorrhage (40%), and preterm contractions (7%). Complications are more common with arterial than venous puncture. In a recent report from Belgium, summarizing 14 years’ experience, 135 intrauterine transfusions were performed in 56 fetuses. There were no fetal or neonatal deaths. Mild adverse events were noted in 10% and severe events in 1.5%. Hydrops and transfusion in a free loop were associated with an increased risk of adverse events whereas gestational age at transfusion after 34 weeks was not. Besides phototherapy, 65% required additional neonatal treatment for alloimmune anemia. Nonhematologic complications occurred in 24% and were mainly related to preterm birth.

PUBS is recommended when the fetus is at substantial risk for severe fetal anemia (MCA-PSV > 1.5 MoM or hydropic), unless the pregnancy is at a gestational age when risks associated with delivery are considered to be less than those associated with the procedure. If it is anticipated that the fetus may require transfusion (e.g., parvovirus infection with elevated MCA Doppler velocity), it is prudent to have crossmatched blood and platelets ready to avoid the risks with a second procedure.

PUBS is usually performed in a setting that allows maternal sedation and intervention for fetal distress after 24 weeks, most often an operating room for labor and delivery. The patient is prepped and steriley drapped and the uterus displaced slightly to the left with appropriate maternal wedging. The ultrasound transducer is draped with a sterile sheath to allow guidance on the sterile field. The patient is often given conscious sedation for comfort and to minimize maternal movement during the procedure. Local anesthetic with lidocaine may be used for patient comfort. Ultrasound guidance may be provided by a second provider or by the operator using a freehand technique. A 20- to 22-gauge needle is typically used, and most often the umbilical vein is targeted at the placental cord insertion (Fig. 41.28). Other approaches include the umbilical vein at the fetal cord insertion or a free loop of cord. The needle position is confirmed by obtaining a blood specimen, ultrasound observation of the needle in the vein, and sonographic streaming within the umbilical vein after injection of saline. Heparinized syringes are used for fetal blood sampling, and values for hemoglobin/hematocrit, platelets, and mean corpuscular volume (MCV) are obtained. The fetal MCV (which should be >100 µm³) is higher than the maternal value and can help confirm fetal origin of the blood sample.

Depending on the insertion site and indication for cordocentesis, fetal paralysis can be considered with vecuronium (0.1 mg/kg estimated fetal weight) or atracurium besylate (0.4 mg/kg estimated fetal weight). Fetal cardiac activity is documented throughout the procedure.

The fetal hematocrit is checked to determine the amount of transfusion needed (Hct < 30% is 2.5th centile >20 weeks). To limit the amount of fluid being transfused into the relatively small circulatory capacity of the fetus, packed RBCs (type O negative; Hct > 90%) are given. The goal is to transfuse to Hct of 40 mL/dL. Successful treatment of anemia with intravascular blood transfusion has been reported as early as 13 weeks’ gestation. When performing PUBS it is important to have a team involved that includes genetic counselors (regarding the underlying cause of anemia), laboratory medicine professionals (to check the MCV and have packed RBCs available), and maternal fetal medicine specialists as well as individuals familiar with guidance for procedures with ultrasound.

When PUBS is not possible, particularly at early gestational age when the umbilical cord is small and difficult to safely
sampling or amniocentesis (Fig. 41.30). This can be both diagnostic (e.g., lymphocyte count in chylothorax or for rapid karyotype) and occasionally therapeutic. Simultaneous sampling does not increase the overall procedure risk.

**Postnatal Investigations**

After birth, the **placenta** should be sent for pathologic analysis, and a **skeletal survey** may be helpful. A geneticist may see the neonate to provide additional input. In cases of death, detailed **autopsy** and placental examination, correlated with antenatal findings, is the best way to determine the cause of nonimmune hydrops. Further investigations may be prompted by additional physical findings at autopsy. If a metabolic condition is suspected as the cause of hydrops, inclusion bodies can be sought on microscopy. In some series the cause of hydrops was identified in only 40% to 50% of patients without autopsy, versus 80% to 90% after postmortem examination.

**FETAL WELFARE ASSESSMENT IN NONIMMUNE HYDROPS**

Noninvasive ultrasound techniques for fetal well-being assessment in pregnancies complicated by nonimmune hydrops include biophysical assessment, pulsed Doppler velocimetry of umbilical and regional fetal vessels, and functional cardiac assessment. Fetal Doppler evaluation may give some indication of anemia, cardiac failure, and well-being. Umbilical vein and intrahepatic vein pulsations, or ductus venosus a-wave reversal, represent cardiac diastolic dysfunction and have been correlated with poor perinatal outcomes.

**OBSTETRIC PROGNOSIS**

The overall **mortality** rate among fetuses with nonimmune hydrops is approximately 70%, with mortality in cases of structural abnormalities not amenable to therapy as high as 100%. In a series of 100 cases of nonimmune hydrops, 74 were thought to have a nontreatable cause, and none of these resulted in a live birth; of 26 with a treatable cause, 18 resulted in a live birth and were alive at 1 year of age. Gestational age at diagnosis of hydrops has been used to predict outcome. A 10-year review of 82 cases presenting after 20 weeks reported an overall mortality rate of 87%, and those diagnosed after 24 weeks were more likely to be idiopathic or related to cardiothoracic abnormalities. Spontaneous resolution of hydrops has been reported in fetuses with normal chromosomes diagnosed before 24 weeks. Although the overall prognosis for fetal hydrops has improved in recent years, most series are small with a mixture of causes and thus are difficult to compare. Some improvement in outcome over earlier reports is attributable to the growing number of cases that are amenable to in utero therapy. Unfortunately, many cases still represent a terminal process. Earlier identification and referral, thorough evaluation, and fetal therapy in appropriate cases are the cornerstone to further improvements in prognosis. Obtaining the best diagnosis is helpful in counseling about recurrence risks.
Maternal Complications (Mirror Syndrome)

Maternal complications may occur in association with fetal hydrops. Hypoproteinemia, edema, weight gain, hypertension, oliguria, and preeclampsia may develop. This association has been termed mirror syndrome because edema in the pregnant patient mirrors that of the hydropic fetus. The syndrome has been described in conjunction with hydrops of various causes. Perinatal mortality and morbidity rates are high. Maternal outcome can be improved by delivery of the fetus and placenta or by fetal intervention to treat the cause of the hydrops. If hydrops cannot be cured, delivery may limit the risk of maternal complications.

Espinoza et al. recently suggested the high plasma concentrations of soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) is implicated in the pathophysiology of mirror syndrome. Hypoxia of the villous trophoblast in cases of villous edema leads to increased production and release of sVEGFR-1 and other antiangiogenic factors into the maternal circulation. Excessive concentrations of these products may be responsible for maternal edema in mirror syndrome.

Delivery

Mode and location of delivery are based on obstetric factors, taking into account the underlying prognosis. Uterine overdistention in severe polyhydramnios carries the risks of placental abruption and cord prolapse after membrane rupture and postpartum hemorrhage from uterine atony. Prematurity secondary to polyhydramnios is a major contributing factor to the poor outcome of some neonates. Therapeutic amniocentesis before induction of labor may be considered in cases with massive polyhydramnios to decrease the risk of malpresentation or cord prolapse. Indomethacin has also been used to decrease the amniotic fluid volume. This drug should be used with caution after 32 weeks’ gestation because of the potential for ductal constriction.
Predelivery Aspiration Procedures

Fetal fluid collections may be drained under ultrasound guidance just before delivery to assist with neonatal resuscitation. This is particularly relevant if large fetal pleural effusions are present. Massive ascites may also be drained to prevent abdominal distocia (when vaginal birth is planned) and aid in fetal breathing when ascites has caused elevation of the diaphragms.

Postnatal Outcome

Because of the high incidence of in utero demise, the cause of hydrops in utero is different from that with a live neonate. In a review of 30 cases of hydrops diagnosed between 10 and 14 weeks of pregnancy, all pregnancies with nonimmune hydrops resulted in abortion, intrauterine fetal death, or pregnancy termination. A 2007 national database review of live-born neonates with hydrops found heart problems (13.7%), abnormalities in heart rate (10.4%), TTTS (9%), congenital anomalies (8.7%), chromosomal abnormalities (7.5%), congenital viral infections (6.7%), isoimmunization (4.5%), and congenital chylothorax (3.2%). Mortality rates were highest among neonates with congenital anomalies (57.7%), and lowest among those with congenital chylothorax (5.9%), and a cause could not be determined in 26%. Factors associated independently with death were younger gestational age, low 5-minute Apgar score, and high levels of support needed the first day after birth. This study reported a 36% death rate before discharge or transfer to another hospital. The severity of hydrops and birth gestational age of the infant are the key determinants for survival. This is important because delivering a fetus early to treat worsening hydrops may not improve survival.

Data are limited regarding long-term outcome of children surviving after hydrops. In one series, 13 in 19 (68%) children surviving beyond 1 year of age were normal; two had mild developmental delay at 1 year of age; one 8-year-old child was mentally retarded; and three (16%) had severe psychomotor impairment with marked growth failure. Haverkamp et al. found that 86% of patients had normal psychomotor development, 86% showed normal neurologic status, 7% had minor neurologic dysfunction, and 4% had spastic cerebral paresis.

CONCLUSION

Hydrops represents a terminal stage for many conditions, the vast majority of which are fetal in origin. The onset of hydrops signifies fetal decompensation. Immune causes can be successfully treated in utero, as can an increasing number of nonimmune causes. Whereas in the past, nonimmune hydrops carried virtually 100% mortality, this is no longer the case. A team approach using obstetric imagers, maternal fetal medicine specialists, neonatologists, and geneticists can help to decide which cases are suitable for therapeutic intervention. A comprehensive approach must be taken to the investigation of hydrops, both for the management of the index case and for future counseling. Cornerstones of this investigation are detailed ultrasound, including echocardiography, fetal karyotyping, and other diagnostic interventions as appropriate, and pathologic examination of the fetus and placenta.

REFERENCES


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