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Fetal Anasarca

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Abstract

Fetal anasarca, defined by the presence of generalized subcutaneous edema measuring >5 mm tissue thickness, is a rare sonographic finding associated with end-stage hydrops fetalis and impending fetal death. This literature review describes the etiology, diagnosis, treatment, and prognosis for both immune and nonimmune hydrops fetalis. Medical technology and treatment have favorably affected fetal mortality associated with hydrops fetalis. Sonography is a noninvasive procedure that is heavily used in the management of hydrops fetalis. Sonographic guidance is equally important in the diagnosis and treatment. Sonographer recognition of early signs that may precipitate fetal anasarca is vital to continued favorable maternofetal outcome.

Keywords

fetal anasarca, hydrops fetalis, nonimmune hydrops

Anasarca is defined as "a generalized infiltration of edema fluid into subcutaneous tissue." The word is derived from the Greek terms *ana*, meaning "through," and *sark*, meaning "flesh."[1] This generalized edema of subcutaneous tissue is an ominous finding that is determined by sonographic examination as >5 mm of tissue thickness (Figures 1–3).[2–5] The sonographic appearance of anasarca "frequently gives the anterior abdominal wall a striking sandwich-like arrangement of thick layers of fluid-filled connective tissue separating thinner layers of muscle."[6] The presence of fetal anasarca is associated with severe hydrops fetalis (HF) and the likelihood of impending fetal demise. However, HF, when found early in the pregnancy and treated accordingly, may result in low fetal mortality/morbidity rates. Since HF is often diagnosed by sonographic examination, it is important that the sonographer is aware of early fetal sonographic findings. The purpose of this literature review is to compare and contrast both immune and nonimmune hydrops. Historical research, etiology, diagnosis and associated findings, clinical implications, and treatment of this condition are discussed.

History

Hydrops fetalis is a condition characterized by any combination and varying amounts of polyhydramnios, placental edema, ascites, pleural effusion, pericardial effusion, and anasarca (Table 1).[2,7–11] This condition was first documented by Ballantyne[12] in 1892. He provided a very concise description of what is now known as severe HF but incorrectly hypothesized that the underlying cause was hereditary. In 1939, Levine and coworkers reported a link between maternal sensitization to a fetal blood group antigen and hydrops fetalis.[13–15] The result was erythroblastosis fetalis, and the condition was labeled *immune hydrops fetalis* (IHF). The following year, Landsteiner and Weiner[16] identified the Rh factor as the sensitizing antigen responsible for IHF. In 1943, however, Potter[17] reported cases where HF was not due to the antigen immunologic response previously described by Landsteiner and Weiner. Consequently, the term *nonimmune hydrops fetalis* (NHF) was given to describe those cases where something other than isoimmunization was the cause for HF. From that time forward, hydrops fetalis has been classified into one of two general categories: immune hydrops fetalis (also known as erythroblastosis fetalis) and nonimmune hydrops fetalis. Although both conditions produce similar fetal characteristics, the underlying causes are quite different and are discussed separately later.

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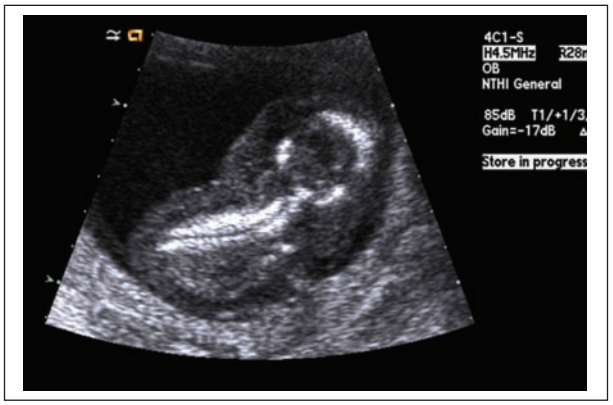

Figure 1. Generalized subcutaneous edema consistent with fetal anasarca.

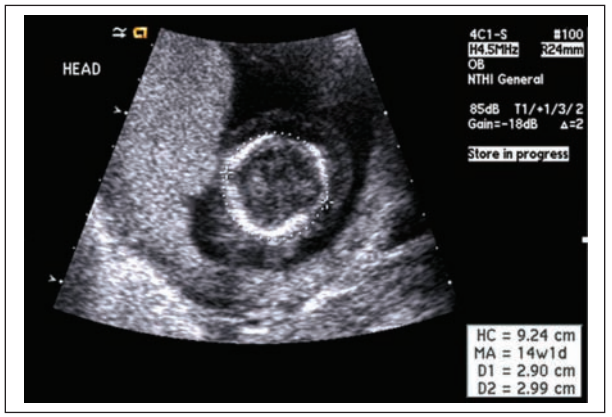

Figure 2. Fetal head circumference measurement demonstrating fetal anasarca.

Immune Hydrops Fetalis

The etiology of IHF is credited to the work of Levine and Stetson,[14] who documented a case study of a woman who had undergone a transfusion of assumed compatible blood after the delivery of a stillborn infant and experienced a reaction to the transfusion. Further investigation revealed the presence of an immune response to an antigen in the mother. It was hypothesized that this response was due to an antigen present in the father but not in the mother. Later researchers were more specifically able to determine that the immune response occurs as a result of the mixing of blood from an Rh-negative mother and Rh-positive fetus. This causes the mother to develop an immunity that will attack fetal Rh-positive blood cells in future pregnancies, resulting in the breakdown of fetal red blood cells and ultimate fetal anemia (erythroblastosis fetalis). The reported incidence of IHF, prior to interventional treatment availability, was approximately 1% of all pregnancies.[18] Of that number, the Rh antigen was responsible for 98% of all cases of IHF.[8] Rarely, IHF has been reported to be the result of ABO blood type incompatibility, which is typically less severe than Rh-negative reactivity.[19,20] In 1968, an Rh immune globulin (RhIG) was developed to prophylactically counter the maternal sensitization response responsible for most cases of IHF. It is estimated that after initiation of RhIG prophylactic treatment, IHF accounts for approximately 10% of all reported cases of fetal hydrops. There is currently no prophylactic treatment available for those cases of IHF that are caused by atypical antibodies other than Rh.[7]

Regardless of the underlying cause for IHF (Table 2), the antigen-antibody reaction is precipitated by a break in the maternal placental barrier, which allows the mother's antibodies to enter the fetal bloodstream. The breakdown of fetal red blood cells can lead to fetal anemia. Fetal bone marrow is primarily responsible for production of red blood cells, but extensive hemolysis triggers a compensatory extramedullary hematopoiesis response. Thus, the liver and splenic tissue is largely overtaken by hematopoietic and fibroblastic tissue. This results in hepatosplenomegaly. As a result, normal hepatic metabolic function is impaired, which can cause portal venous hypertension and eventual fetal ascites. Concurrently, the edematous placenta becomes enlarged due to umbilical venous hypertension. The inability

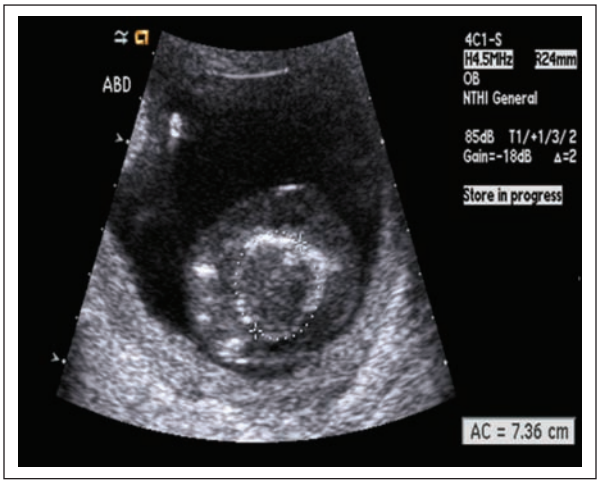

Figure 3. Fetal abdominal circumference measurement demonstrating fetal anasarca.

Table 1. Sonographic Characteristics of Hydrops Fetalis

Polyhydramnios—often the first sonographic finding
Placental edema >5 cm thickness
Ascites—best viewed between liver and abdominal wall
Pleural and/or pericardial effusion[a]
Anasarca[b]—generalized subcutaneous tissue >5 mm thickness

[a]Found in varying combination and amounts.
[b]Indicator of chronic/severe hydrops fetalis.

Table 2. Conditions Associated With Hydrops Fetalis

Immune Hydrops Fetalis	Nonimmune Hydrops Fetalis
Maternal Rh incompatibility Maternal ABO incompatibility	Other than maternal blood incompatibility • Abnormal cardiac structure/function • Aneuploidy • Hematologic disease • Twin-twin transfusion • Congenital infections • Cystic hygroma/lymph obstruction • Thoracic compression • Urinary tract obstruction • Prune-belly syndrome • Metabolic disorders • Skeletal dysplasias • Idiopathic

Table 3. Pathophysiology of Immune Hydrops Fetalis

- Maternal antibodies enter fetal bloodstream
- Antibodies attack and break down fetal red blood cells (hemolysis)
- Fetal response is increased blood cell production in bone marrow (hematopoiesis)
- Extensive hemolysis triggers compensatory production of blood cells in liver and spleen (extramedullary hematopoiesis)
- Liver/spleen are overtaken by hematopoetic and fibroblastic tissue leading to organ enlargement (hepato/splenomegaly)
- Liver's impaired normal metabolic function leads to portal venous hypertension
- Portal venous hypertension contributes to accumulation of fluid in the fetal peritoneum (ascites)
- Umbilical venous hypertension produces placental edema
- Compromised liver and placental protein synthesis result in hypoproteinemia
- Hypoproteinemia triggers increased cardiac output
- Severe hypoproteinemia exceeding cardiac output function causes reduced tissue oxygenation (hypoxia), which triggers capillary dilation and increased permeability
- Result is redistribution of body fluid balance at intracellular, intravascular, and interstitial levels

of the fetal liver and placenta to adequately perform protein synthesis and disperse amino acids leads to fetal hypoproteinemia. The fetal response to hypoproteinemia is increased cardiac output. Depending on the severity of the condition, if the cardiac output cannot provide adequate fetal tissue oxygenation, hypoxia and acidosis occur, which then triggers capillary dilation and increased permeability. This trio of physiologic events (hypoproteinemia, increased venous pressure, and increased capillary permeability) reduces the oncotic pressure and allows for redistribution of the normal body fluid balance at the intracellular, intravascular, and interstitial levels into the fetal body cavity (Table 3).[4,8]

Nonimmune Hydrops Fetalis

NHF, first described by Potter[17] in 1943, is the presence of hydrops fetalis due to underlying factors other than materno-fetal Rh incompatibility (Table 2). When first reported, less than 20% of all hydrops fetalis cases fell into the NHF category. After the introduction and initiation of immunoglobulin prophylaxis for IHF, however, the NHF category has increased to include approximately 90% of all hydrops fetalis occurrences.[7,8,20] Although there is agreement on the percentage of incidence for NHF, the ratios for incidence range from 1/1500 to 1/4000 pregnancies.[7,8,21] Because there is no specific test to diagnose NHF, careful sonographic screening for fetal abnormalities is key to early detection and appropriate treatment.

The underlying etiology of NHF is poorly understood and has been related to a variety of underlying conditions.[22] In North America, NHF is most commonly associated with cardiac arrhythmias and/or structural malformation. Cardiac contractility, as a result of abnormal cardiac structure or function, can lead to heart failure and eventual hydrops. Chronic or progressive hydrops associated with cardiac structural anomalies is nearly 100% fatal. Outcomes associated with arrhythmias can often be managed in utero and will be discussed later. Next most common in occurrences is aneuploidy. NHF associated with chromosomal fetal anomalies is nearly 100% fatal. Hematologic diseases (especially alpha thalassemia), twin-twin transfusion, and congenital infections are also commonly cited, although less frequently, as underlying causes for NHF. With early detection, this group of conditions has a much better mortality rate. Sohaey[7] suggests a survival rate of 75% when treating for nonimmune fetal anemia after onset of hydrops compared with 95% when treated prior to development of NHF. Twin-twin transfusion is associated with high cardiac output and failure. Fetal congenital infection sources are numerous, but the most commonly cited is parvovirus. Fetal infections are commonly associated with myocarditis and anemia.[7,9,23] Multiple other disorders have also been cited to be associated with NHF. Although not exhaustive, the list includes cystic hygroma and associated lymphatic obstructions; thoracic compression (cystic adenomatoid malformation, diaphragmatic hernia); urinary tract obstruction, prune-belly syndrome, trisomy 13, 18, and 21; triploidy; Turner's 45,X syndrome; TORCH infections;

metabolic disorders; and skeletal dysplasias. Despite this extensive but not inclusive list of underlying etiologies, NHF is of idiopathic origin in as many as 30% to 80% of occurrences.[7,9,24–34] Although dismal outcomes are often the case, instances of spontaneous resolution of sonographically severe NHF have been reported.[35–38]

A number of nonfetal conditions may be associated with NHF, although not as prevalent as that of fetal origination. Those most commonly cited include maternal diabetes mellitus, severe anemia and/or hypoproteinemia, placental chorioangioma, placental venous thrombosis, and cord torsion, knot, or tumor.[7,9,24,39] Because NHF "represents the terminal stage for many conditions," there is no predictable sequence of events that results in the transfer of fetal body fluids. Animal studies thus far have failed to provide the exact reason(s) for the systemic failures that lead to NHF. Fluid exchange pathways in the fetus are primarily transplacental, transmembranous, and transcutaneous. A hydrostatic imbalance allows fluid to collect in the intravascular, intracellular, and interstitial compartments. Perhaps transcutaneous exchange is the major initial pathway until such time as the lymph system and fetal kidneys can assume adequate fluid elimination function. There is no consensus on the mechanisms that result in polyhydramnios and an edematous placenta, which is almost always present, as well.[15,22]

Diagnosis of Hydrops Fetalis

The primary intervention for hydrops fetalis prevention is a thorough prenatal maternal history to include age, racial background, occupation, and medical history. This information alone may place the pregnancy in a potential high-risk category. For example, Asians are more prone to alpha-thalassemia, and sickle cell anemia is more prevalent in blacks. School teachers also are more susceptible to childhood illnesses such as parvovirus B19, rubella, and so on. Those who are in their teens or older than age 40 years those taking medications, and those with maternal conditions such as hypertension, diabetes, and systemic lupus erythematosus are all conditions to be noted and monitored closely. Family history, including maternal and paternal genetic information, should also be documented.

The mother should undergo a panel of serologic screening tests to include ABO and blood type, indirect Coombs test, complete blood count, glucose, TORCH/HPVB19, VDRL, HIV, IgM, and IgG. Serologic testing can rule out immune hydrops fetalis with a high degree of accuracy. There is no maternal serologic test that can produce the same level of confidence, however, to rule out NHF.

Regardless of the serologic tests, a diagnostic sonographic fetal anatomy screening examination may provide initial findings consistent with hydrops fetalis and indications that the pregnancy may be at risk. The pregnancy may be uneventful in as high as 30% of hydrops fetalis cases.[8] One of the first warning signs may be increased uterine size for pregnancy dating. Polyhydramnios has a recorded prevalence in up to 75% of fetuses with hydrops fetalis.[40] Rarely, however, oligohydramnios is found with underlying NHF conditions such as homozygous alpha-thalassemia and severe lymphangiectasia.[8] Placental thickness of >5 cm is also an abnormal finding and warrants a detailed fetal anatomy evaluation. In the presence of any of the above findings, the fetus should be carefully evaluated for evidence of ascites (best viewed in the space between the liver and abdominal wall), pericardial and/or pleural fluid, and cardiac arrhythmia and/or structural abnormality. Anasarca (generalized edema of fetal subcutaneous tissue measuring 5 mm or greater) is typically a finding associated with chronic/severe hydrops and increased mortality rates. Other sonographic findings that may be encountered (although not specific to hydrops fetalis) include hepatosplenomegaly, cardiomegaly, and umbilical vein dilation.[2] It should be noted that hydrops by definition would include at least two body cavity fluid accumulations. However, identification of only one cavity fluid accumulation does not eliminate hydrops fetalis as a differential diagnosis.[22]

Prognosis and Treatment

The general prognosis for NHF is dismal. In a series of 79 cases of nonimmune fetal ascites, Favre et al[41] report a mortality rate of 78% with ascites diagnosed before 24 weeks' gestation compared with a 45% mortality rate after 24 weeks. Findings consistent with NHF, in addition to ascites, lower survival rates to 33% compared with 49% for those who do not have the associated findings. Amniotic fluid volume was not a significant indicator of survival in this study, ranging from 53% to 33% survival rates for normal amniotic fluid volume, poly- or oligohydramnios. Hydrops fetalis in addition to fetal anomalies carries an extreme likelihood for fetal mortality. Nevertheless, as stated before, there have been reported cases of spontaneous resolution of NHF.[35–38]

Sonographic-guided amniocentesis for fetal karotype is beneficial in determining the degree of aggressive treatment. On the other hand, findings consistent with alpha-thalassemia, infection, glycogen storage disease, or nephrosis will serve to direct appropriate treatment and delivery plans. Aspiration of fetal cord blood is an alternative method for obtaining the same results in a quicker timeframe but with greater risk. Fetal cardiac imaging with m-mode is useful for determining arrhythmia and cardiac deformity. Treatment for arrhythmias, in the absence of cardiac deformity, has produced favorable outcomes with digoxin, verapamil, adenosine, procainamide, amiodarone, and flecainide transplacental or direct fetal drug administration. There have also been limited reports of hydrops reversal with in utero thoracoamniotic shunt placement. This

procedure is especially indicated to reduce the incidence of pulmonary hypoplasia. Therapeutic pulmonary effusion drainage may also be indicated prior to delivery to facilitate resuscitation. In utero management of twin-twin transfusion does not enjoy a high success rate, but amniocentesis to reduce fluid volume and embryoscopic laser vessel ablation procedures are being performed with promising outcomes. In utero antibiotic therapy for infections, especially parvovirus B19, has proven to be effective, though.[22–24,42–45]

There continues to be improved fetal morbidity and mortality associated with early diagnosis and treatment with Rh immunoglobulin injections administered with each pregnancy or invasive procedures during the pregnancy. Suggested protocol is RhIG administration at 28 weeks' gestation in the unsensitized Rh-negative patient and another administration postdelivery if the fetus is Rh positive. Prenatal monitoring may include antibody titers, amniotic fluid analysis, and serial sonographic fetal assessment. Depending on the severity of findings, treatment can range from minimal postnatal treatment to intrauterine transfusion.[15,18]

Fetal anemia can be associated with both IHF and NHF, necessitating fetal transfusion for survival. Associated risks for intrauterine transfusion are a point of consideration with a reported 70% to 85% survival rate.[24] Middle cerebral artery Doppler can be used to noninvasively assess fetal anemia. This procedure requires a high degree of operator accuracy and cannot yet be considered the "gold standard" against fetal blood sampling for the delta optical density 450 (OD450) bilirubin assessment test.[46,47]

Delivery of infants affected with hydrops fetalis should be prearranged at a facility prepared to provide the necessary care for high-risk infants. The goal is to delay until 38 weeks' gestation or until such time that the risk of prematurity favors the risk of continued intrauterine transfusion. There appears to be no consensus on the preference for vaginal versus cesarean section delivery. Labor inducement and vaginal delivery are always the goal and often successfully accomplished. Cesarean delivery is indicated if breech position or labor is complicated by large fetal and/or placental size, fetal heart rate variances, and delivery prior to 32 weeks' gestation.[15,18] Despite overall grim outcomes, good outcomes have been reported with hydrops fetalis survivors.[48]

Maternal Risks

Hydrops fetalis is not without risk to the mother as well. Polyhydramnios is the most common maternal complication, which may lead to placental abruption, premature membrane rupture, and premature labor. Pregnancy-induced hypertension is the next most common reported complication, which has the potential to progress to preeclampsia and eclampsia, rendering significant maternal risk. Other associated maternal complications include anemia, hypoalbuminemia, and to a lesser degree, urinary tract infections, antepartum hemorrhage**,** and gestational diabetes. Invasive procedures provide an increased risk of placental abruption, and peripartum concerns include dystocia, cesarean delivery, postpartum hemorrhage, and retained placenta.[22] On rare occurrences, cases of Ballantyne syndrome (also known as mirror syndrome or triple edema) have been reported. Ballantyne syndrome is characterized by fetal hydrops, placental hydrops**,** and maternal edema. The underlying pathophysiology of this unusual syndrome is unclear but believed to be associated with the enlarged placenta.[49,50]

Conclusion

Fetal anasarca, defined by the presence of generalized subcutaneous edema measuring >5 mm tissue thickness, is an indication of end-stage hydrops fetalis, and fetal death is the expected outcome. Therefore, early detection and treatment are a critical fetal morbidity and mortality component. Adverse outcomes related to IHF have been significantly reduced via serologic testing, immunoglobulin therapy, and aggressive in utero treatment. Timing and extent of treatment are largely determined from ongoing diagnostic sonographic examination findings.

NHF currently represents approximately 90% of all hydrops fetalis diagnoses. Because of the wide variety of etiologies, no specific "early warning signs" associated with NHF have been established. A fetal sonography examination performed because of a clinical finding of "large for gestational age" may be the first indication of findings consistent with NHF. It is imperative that every fetal sonography examination is carefully scrutinized for evidence of polyhydramnios, placental thickening, fetal ascites, pleural and/or pericardial fluid, and subcutaneous tissue thickness. Evidence of any of the above should lead to careful intentional fetal sonographic examination to rule out associated anomalies.

Sonography is a noninvasive procedure that is heavily used in the management of hydrops fetalis. Sonographic guidance is equally important in the diagnosis and treatment. Medical technologic and treatment advances have favorably affected fetal mortality associated with hydrops fetalis. Thus, fetal anasarca has become a rare sonographic finding. Sonographer recognition of early signs that may precipitate anasarca is vital to continued favorable maternofetal outcome.

Declaration of Conflicting Interests

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