Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline #7: nonimmune hydrops fetalis

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OBJECTIVE: Nonimmune hydrops is the presence of ≥2 abnormal fetal fluid collections in the absence of red cell alloimmunization. The most common etiologies include cardiovascular, chromosomal, and hematologic abnormalities, followed by structural fetal anomalies, complications of twinning, infection, and placental abnormalities. We sought to provide evidence-based guidelines for the evaluation and management of nonimmune hydrops fetalis.

METHODS: A systematic literature review was performed using MEDLINE, PubMed, EMBASE, and Cochrane Library. The search was restricted to English-language articles published from 1966 through June 2014. Priority was given to articles reporting original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Evidence reports and guidelines published by organizations or institutions such as the National Institutes of Health, Agency for Health Research and Quality, American Congress of Obstetricians and Gynecologists, and Society for Maternal-Fetal Medicine were also reviewed, and additional studies were located by reviewing bibliographies of identified articles. Grading of Recommendations Assessment, Development, and Evaluation methodology was employed for defining strength of recommendations and rating quality of evidence. Consistent with US Preventive Task Force guidelines, references were evaluated for quality based on the highest level of evidence.

RESULTS AND RECOMMENDATIONS: Evaluation of hydrops begins with an antibody screen (indirect Coombs test) to verify that it is nonimmune, detailed sonography of the fetus(es) and placenta, including echocardiography and assessment for fetal arrhythmia, and middle cerebral artery Doppler evaluation for anemia, as well as fetal karyotype and/or chromosomal microarray analysis, regardless of whether a structural fetal anomaly is identified. Recommended treatment depends on the underlying etiology and gestational age; preterm delivery is recommended only for obstetric indications including development of mirror syndrome. Candidates for corticosteroids and antepartum surveillance include those with an idiopathic etiology, an etiology amenable to prenatal or postnatal treatment, and those in whom intervention is planned if fetal deterioration occurs. Such pregnancies should be delivered at a facility with the capability to stabilize and treat critically ill newborns. The prognosis depends on etiology, response to therapy if treatable, and the gestational age at detection and delivery. Aneuploidy confers a poor prognosis, and even in the absence of aneuploidy, neonatal survival is often <50%. Mirror syndrome is a form of severe preeclampsia that may develop in association with fetal hydrops and in most cases necessitates delivery.

Key words: fetal complications, hydrops, nonimmune hydrops fetalis

Hydrops fetalis is a Greek term that describes pathological fluid ("ὕδωρ," Greek for water) accumulation in fetal soft tissues and serous cavities. The features are detected by ultrasound, and are defined as the presence of ≥2 abnormal fluid collections in the fetus. These include ascites, pleural effusions, pericardial effusion, and generalized skin edema (defined as skin thickness >5 mm).[1] Other frequent sonographic findings include placental thickening (typically defined as a placental thickness ≥4 cm in the second trimester or ≥6 cm in the third trimester)[2,3] and polyhydramnios (Figure 1). Nonimmune hydrops fetalis (NIHF) refers specifically to cases not caused by red cell alloimmunization. With the development and widespread use of Rh(D) immune globulin, the prevalence of Rh(D) alloimmunization and associated hydrops has dramatically decreased. As a result, NIHF now accounts for almost 90% of cases of hydrops,[4] with the prevalence in published series reported as 1 in 1700-3000 pregnancies.[5-7] However, many of these reports predate routine sonography and limited information is available on contemporary incidence of NIHF in a prenatal population.

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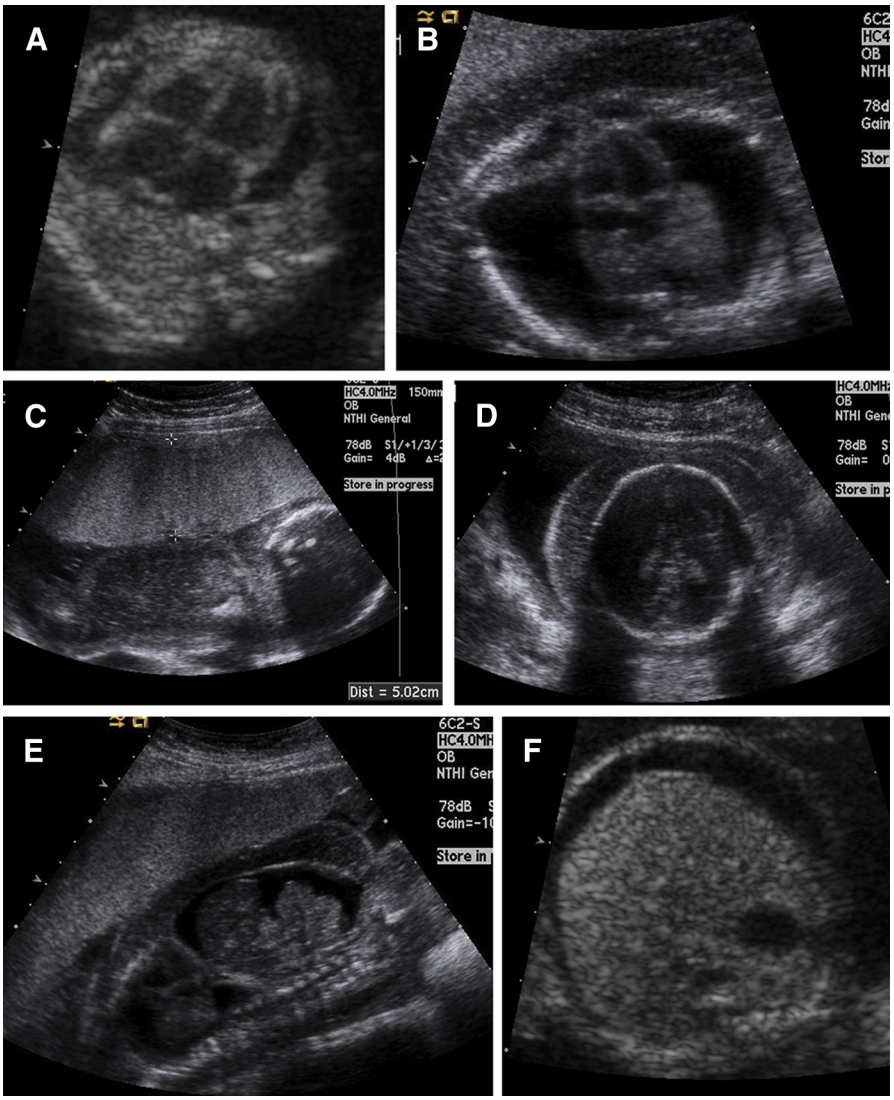
What is the underlying pathogenesis of NIHF?

The common pathophysiology underlying the many etiologies of hydrops fetalis is an imbalance in the regulation of

FIGURE 1
Sonographic features of hydrops fetalis



A, Pericardial effusions. **B**, Pleural effusions; note midline heart anterior to small lungs with bilateral effusions. **C**, Placental thickening, with placenta measuring >4 mm in thickness. **D**, Skin thickening at level of fetal skull. **E**, Ascites, sagittal, with free-floating loops of bowel surrounded by ascites. **F**, Ascites in upper abdomen, at level of fetal liver and stomach.

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fluid movement between the vascular and interstitial spaces,[8] with an increase in interstitial fluid production or a decrease in lymphatic return. Various mechanisms thought to lead to NIHF include increased right heart pressure, resulting in increased central venous pressure (eg, structural heart defects); obstruction of venous or arterial blood flow (eg, pulmonary masses); inadequate diastolic ventricular filling (eg, arrhythmias); hepatic venous congestion leading to decreased hepatic function and hypoalbuminemia; increased capillary permeability (eg, congenital infection); anemia leading to high output cardiac failure and extramedullary hematopoiesis, often with resultant hepatic dysfunction; lymphatic vessel dysplasia and obstruction (eg, cystic hygroma); and reduced osmotic pressure (eg, congenital nephrosis). The precise pathogenesis of NIHF depends on the underlying disorder, and in many cases remains unclear. Pathophysiologic mechanisms that contribute to the development of hydrops are described in Table 1 according to underlying etiology or category.

What are the causes of NIHF?

NIHF can result from a large number of underlying pathologies (Table 1). The differential diagnosis is extensive, and the success in identifying a cause partially depends on the thoroughness of efforts to establish a diagnosis. Although older studies considered many cases to be idiopathic,[9-11] more recent, larger series and a systematic review report that a cause can be found in nearly 60% of cases prenatally[12] and in 85% when postnatal detection is included.[13]

A number of series have been published describing the many disorders associated with NIHF.[8,13-16] Review of these indicates that the most common etiologies of NIHF include cardiovascular causes, chromosomal anomalies, and hematologic abnormalities. Other conditions associated with NIHF include fetal malformations, particularly thoracic abnormalities, twin-twin transfusion syndrome, congenital infection, placental abnormalities, fetal tumors, and genetic or metabolic disorders (Table 1).

Overall, *cardiovascular abnormalities* are the most common cause of NIHF in most series, accounting for about 20% of cases.[13] NIHF can result from cardiac structural abnormalities, arrhythmias, cardiomyopathy, cardiac tumors, or vascular abnormalities. In most cardiac cases, hydrops is likely caused by increased central venous pressure due to a structural malformation or from inadequate diastolic ventricular filling.[8,17] The most common congenital heart defects reported in association with NIHF are right heart defects.[6,14,18] The prognosis of NIHF due to cardiac structural abnormalities is poor, with combined fetal and infant mortality reported as 92%, largely due to the severity of the heart defects that cause in utero congestive heart failure.[19]

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Both tachyarrhythmias and bradyarrhythmias can lead to NIHF.[14,20] The most common tachyarrhythmias are supraventricular tachycardia and atrial flutter, and both can often be successfully treated with transplacental medical therapy.[14,19,20] We recommend maternal treatment with antiarrhythmic medications for NIHF secondary to fetal tachyarrhythmia unless the gestational age is close to term or there is a maternal or obstetrical contraindication. Medication selection and dosing are reviewed elsewhere.[21]

Fetal bradycardia is most commonly caused by congenital heart block, which may occur secondary to an immune etiology such as transplacental passage of anti-Sjogren's-syndrome-related antigen A, also called anti-Ro, or the combination anti SSA/Ro or anti Ro/SSA antibodies associated with maternal autoimmune disease. It may also result from structural abnormalities affecting cardiac conduction, as with endocardial cushion defects in the setting of a heterotaxy syndrome. Once third-degree atrioventricular block has developed, treatment with corticosteroid therapy has not been shown to be beneficial, and in the setting of hydrops the prognosis is poor.[22] For this reason, in-utero therapy for fetal bradyarrhythmia resulting in hydrops is considered investigational and is not generally recommended outside of a research setting.

TABLE 1
Etiologies of nonimmune hydrops fetalis[6,11,12,14,75]

Cause	Cases	Mechanism
Cardiovascular	17-35%	Increased central venous pressure
Chromosomal	7-16%	Cardiac anomalies, lymphatic dysplasia, abnormal myelopoiesis
Hematologic	4-12%	Anemia, high output cardiac failure; hypoxia (alpha thalassemia)
Infectious	5-7%	Anemia, anoxia, endothelial cell damage, and increased capillary permeability
Thoracic	6%	Vena caval obstruction or increased intrathoracic pressure with impaired venous return
Twin-twin transfusion	3-10%	Hypervolemia and increased central venous pressure
Urinary tract abnormalities	2-3%	Urinary ascites; nephrotic syndrome with hypoproteinemia
Gastrointestinal	0.5-4%	Obstruction of venous return; gastrointestinal obstruction and infarction with protein loss and decreased colloid osmotic pressure
Lymphatic dysplasia	5-6%	Impaired venous return
Tumors, including chorioangiomas	2-3%	Anemia, high output cardiac failure, hypoproteinemia
Skeletal dysplasias	3-4%	Hepatomegaly, hypoproteinemia, impaired venous return
Syndromic	3-4%	Various
Inborn errors of metabolism	1-2%	Visceromegaly and obstruction of venous return, decreased erythropoiesis and anemia, and/or hypoproteinemia
Miscellaneous	3-15%	
Unknown	15-25%	

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Chromosomal abnormalities, particularly Turner syndrome (45,X) and Down syndrome (trisomy 21) are also common causes of NIHF, accounting for 13% in a large systematic review.[13] In prenatal series, aneuploidy is the most common cause of NIHF, particularly when identified early in gestation.[4,5,12] Turner syndrome is associated with 50-80% of cases of cystic hygromas, which result from a lack of communication between the lymphatic system and venous drainage in the neck.[23] Lymphatic dysplasia likely leads to the development of NIHF in these cases.

NIHF has been described in association with other aneuploidies, including trisomies 13 and 18, and triploidy.[24-27] In some cases, hydrops occurs due to cardiovascular malformations in aneuploid fetuses. NIHF has also been reported in trisomy 21 in the absence of structural heart defects.[24,25,27,28] Some such cases occur due to a transient abnormal myelopoiesis, a leukemic condition that occurs in about 10% of infants with Down syndrome.[25,27] Postnatally, transient abnormal myelopoiesis is often mild and self-limiting; prenatally, it is less common but typically more severe. For these reasons, we recommend that NIHF is an indication to offer prenatal diagnosis with karyotype, fluorescence in situ hybridization, and/or chromosomal microarray analysis, even when severe anemia is present (Figure 2). Screening with noninvasive prenatal testing may detect some chromosomal causes but provides more limited information about possible genetic etiologies, and therefore we recommend diagnostic testing.

Fetal anemia, which can result in immune hydrops if caused by blood group alloimmunization, can also lead to NIHF. Etiologies include inherited conditions such as hemoglobinopathies, as well as acquired conditions, such as hemolysis, fetomaternal hemorrhage, parvovirus infection, or red cell aplasia.

Among the hemoglobinopathies, the most common cause of NIHF is alpha thalassemia. This autosomal recessive disorder is common in Southeast Asian populations, where it accounts for 28-55% of NIHF.[29,30] The incidence in most other series of NIHF is about 10%.[13] Parents can be screened by evaluation of the mean cell volume, which will be <80 fL in thalassemia carriers. Definitive

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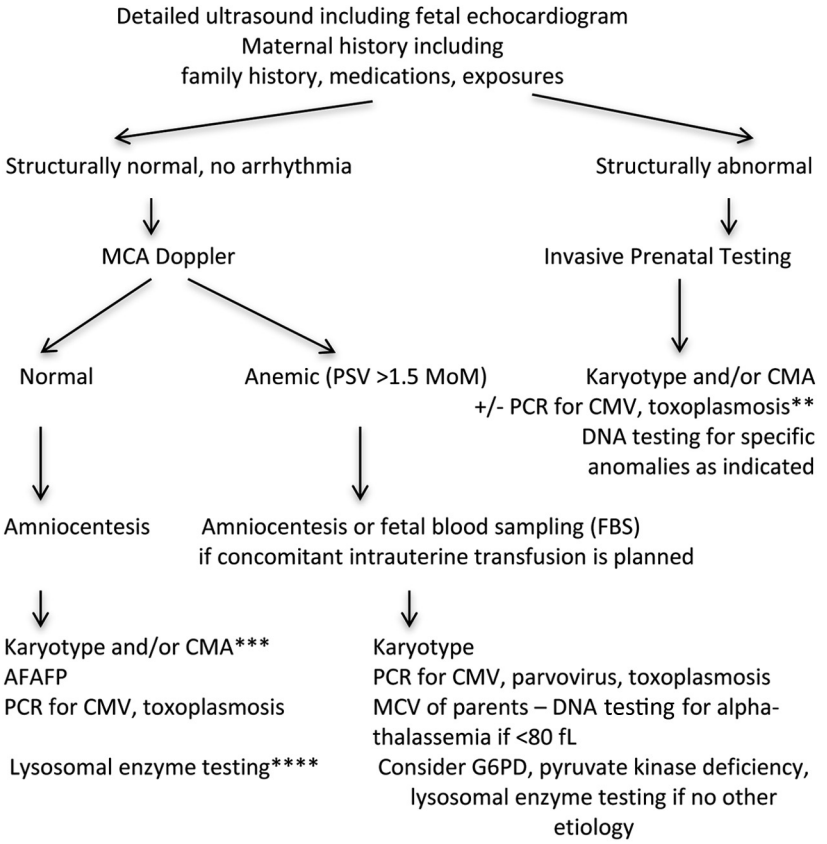
FIGURE 2
Workup of nonimmune hydrops fetalis



AFAFP, amniotic fluid alpha fetoprotein; *CBC*, complete blood count; *CMA*, chromosomal microarray; *CMV*, cytomegalovirus; *G6PD*, glucose-6-phosphate dehydrogenase deficiency; *MCA PSV*, middle cerebral artery peak systolic velocity; *MCV*, mean corpuscular volumne; *MoM*, multiple of the median; *PCR*, polymerase chain reaction; *RPR*, rapid plasma reagin.

*Assuming negative indirect Coombs test, thereby excluding alloimmunization; **CMV/toxoplasmosis testing if fetal anomalies suggestive of infection; ***Either amniocentesis or FBS; ****Available in some laboratories.[67,76]

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diagnosis of an affected fetus can be made by detection of one of the common DNA deletions or point mutations that account for most cases.[31] Conversely, a fetal blood sample can be evaluated for the presence of the abnormal Bart's hemoglobin seen in this condition. Bart's hemoglobin is an ineffective oxygen carrier, thus the fetus with alpha thalassemia will suffer severe intrauterine hypoxia from an early gestational age. The resultant NIHF will typically present in the late second or early third trimester.

Fetal anemia may also occur due to *fetal hemorrhage*. NIHF occurs only with significant fetomaternal bleeding that is not enough to lead to fetal hypovolemia and death. Fetomaternal hemorrhage leading to hydrops may occur as either an isolated acute event, or as a chronic, ongoing hemorrhage.[32,33] With either, a Kleihauer-Betke smear will show the presence of fetal cells in the maternal peripheral blood in most cases. Flow cytometry can also be used to estimate the volume of fetal bleeding into the mother. This is an important diagnosis to make, because even with a massive fetomaternal hemorrhage, intravascular fetal transfusion can be lifesaving.[34-36] For this reason, we recommend that NIHF due to anemia from fetomaternal hemorrhage be treated with transfusion, unless the pregnancy is at an advanced gestational age and risks associated with delivery are considered to be less than those associated with the procedure.

Other, less common causes of fetal anemia and hydrops include G-6-PD deficiency, erythrocyte enzymopathies such as pyruvate kinase deficiency, and maternal acquired red cell aplasia.[37,38]

NIHF has been reported in association with a number of viral, bacterial, and parasitic *infectious diseases*, including parvovirus, cytomegalovirus, syphilis, and toxoplasmosis.[39-42] In most series, such infections account for 5-10% of NIHF.[6,13,14,16] Although the associations are less clear, NIHF has also been reported to occur with Coxsackie virus, trypanosomiasis, varicella, human herpesvirus 6 and 7, herpes simplex type 1, respiratory syncytial virus, congenital lymphocytic choriomeningitis virus, and leptospirosis.[6,43-47] Fetal infection can cause NIHF due to anemia, anoxia, endothelial cell damage, increased capillary permeability, and myocarditis.

Parvovirus is the most commonly reported infectious cause of NIHF. In the fetus, the virus has a predilection for erythroid progenitor cells, leading to inhibition of erythropoiesis and subsequent anemia.[48,49] The risk of a poor outcome for the fetus is greatest when the congenital infection occurs in the early second trimester (<20 weeks of gestation).[50-53] The risk of fetal death has been reported to be 15% at 13-20 weeks of gestation, and 6% after 20 weeks.[54] In most cases, the anemia is transient and fetal intravascular transfusion can support a fetus through this aplastic crisis.[55,56] However, development of NIHF is associated with high mortality, and outcomes are reported to be significantly improved following fetal intrauterine transfusion.[51,53] For this reason, we recommend fetal intrauterine transfusion for NIHF due to parvovirus infection, unless the pregnancy is at an advanced gestational age and risks associated with delivery are considered to be less than those associated with the procedure.

Fetal thoracic abnormalities, including masses as well as congenital hydrothorax, can also be associated with NIHF. The most frequent pulmonary lesion associated with NIHF is a congenital pulmonary airway malformation (CPAM).

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With a large lesion or effusion, mediastinal shift may impair venous return and cardiac output, and the associated esophageal compression may result in polyhydramnios. Hydrops occurs in only about 5% of fetuses with CPAM but confers a poor prognosis without treatment.[57] If the lesion is macrocystic, the cyst may be treated with needle drainage or thoracoamniotic shunt placement.[58,59] If predominantly solid (microcystic), both corticosteroid therapy and in utero resection have been advocated, and corticosteroid treatment is currently recommended as a first-line treatment.[60] Large bronchopulmonary sequestrations have also been treated with a needle procedure involving neodymium:yttrium-aluminium-garnet laser of the feeding vessel.[57]

The most common etiology of an isolated effusion leading to NIHF is chylothorax, caused by lymphatic obstruction. The fluid may be sampled at the time of needle drainage or shunt placement, and the diagnosis is confirmed by the finding of a fetal pleural cell count with >80% lymphocytes in the absence of infection. Reported survival exceeds 50% in hydropic fetuses treated with thoracoamniotic shunt placement.[61]

Twin-twin transfusion syndrome results from an imbalance in blood flow caused by anastomoses in the placentas of monochorionic twin pregnancies. In severe cases, one or both twins may develop NIHF, although more commonly the recipient twin is affected, likely due to hypervolemia and increased central venous pressure.[62] Cases of twin-twin transfusion sequence with hydrops have a very poor prognosis without treatment, and laser therapy is considered by most experts to be the best available therapeutic approach to improve the prognosis.[63] Selective termination via umbilical cord coagulation is also an option for pregnancies with twin-twin transfusion sequence resulting in NIHF. Another complication of monochorionic twinning that may result in NIHF is twin-reversed arterial perfusion sequence. Radiofrequency ablation of the acardiac twin has been advocated for severe cases, including those with hydrops, with reported overall survival of 80%.[64]

Structural *urinary and gastrointestinal abnormalities* are less common causes of NIHF. A ruptured bladder or renal collecting system may cause urinary ascites and mimic NIHF. Congenital nephrotic syndromes have been reported to cause NIHF due to hypoproteinemia.[19,65,66] Surviving infants may have massive proteinuria at birth and develop renal failure in childhood.

Few primary abnormalities of the gastrointestinal tract have been associated with NIHF. Those that have been reported include diaphragmatic hernia, midgut volvulus, gastrointestinal obstruction, jejunal atresia, malrotation of the intestines, and meconium peritonitis.[6,19] Intraabdominal masses may cause NIHF due to obstruction of venous return, while gastrointestinal obstruction and infarction may lead to decreased colloid osmotic pressure due to protein loss.[19] Hepatic disorders such as cirrhosis, hepatic necrosis, cholestasis, polycystic disease of the liver, and biliary atresia have been reported in association with NIHF, most likely due to hypoproteinemia.[7] Hemangioma of the liver has also been reported as a cause of NIHF, probably due to arteriovenous shunting resulting in cardiac failure.

Neoplastic diseases or fetal tumors can occur in utero and have been associated with NIHF. Relatively common in this category are lymphangiomas, hemangiomas, sacrococcygeal, mediastinal, and pharyngeal teratomas, and neuroblastomas.[19,67,68] Many of these are very vascular and lead to NIHF due to high output cardiac failure. Fetal therapy has been offered for cases of solid sacrococcygeal teratoma resulting in NIHF, and in a recent systematic review, open fetal surgery resulted in survival in 6 of 11 cases (55%), and minimally invasive therapy was associated with survival in 6 of 20 (30%).[69] Tuberous sclerosis is an autosomal dominant disorder characterized by fibroangiomatous tumors in multiple organs, most typically the cortex of the brain, the skin, and the kidneys. Cardiac rhabdomyomas and liver fibrosis are also sometimes present. NIHF has been reported in association with tuberous sclerosis, probably either as a result of cardiac failure due to rhabdomyomas (resulting in obstruction to filling or outflow), or hepatic failure due to fibrosis.[70]

Placental and cord lesions that have been associated with NIHF include chorioangiomas, angiomyxoma of the cord, aneurysm of the umbilical artery, cord vein thrombosis, umbilical vein torsion, true knots, and amniotic bands.[7,19,68] Placental chorioangiomas are relatively common, occurring in about 1% of pregnancies. While small lesions are usually not clinically significant, those measuring >5 cm can act as high volume arteriovenous shunts and lead to hydrops due to high output cardiac failure. Other vascular tumors and arteriovenous malformations can similarly cause NIHF. Hemangiomas have been reported to cause NIHF, likely due to severe anemia, hypoproteinemia, and/or extramedullary erythropoiesis.

A large number of *skeletal dysplasias* have been associated with NIHF, including achondroplasia, achondrogenesis, osteogenesis imperfecta, osteopetrosis, thanatophoric dysplasia, short-rib polydactyly syndrome, and asphyxiating thoracic dysplasia.[14,19,71-73] In all of these, the mechanism is unclear, although it has been proposed that hepatic enlargement occurs secondary to intrahepatic proliferation of blood cell precursors to compensate for a small bone-marrow volume. This may cause large vessel compression and lead to anasarca in these fetuses.

Inborn errors of metabolism and other genetic conditions are historically associated with 1-2% of cases of NIHF, which may be transient or manifest as isolated ascites. Inherited metabolic disorders that have been implicated as a cause of NIHF are most typically lysosomal storage diseases such as various mucopolysaccharidoses, Gaucher disease, and Niemann-Pick disease.[74,75] In a recent review of the literature including 678 cases of NIHF, lysosomal storage diseases occurred in 5.2% of all NIHF cases, and in 29.6% of idiopathic NIHF cases if a comprehensive workup for these conditions is done.[76] Proposed mechanisms

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involve visceromegaly and obstruction of venous return, decreased erythropoiesis and anemia, and/or hypoproteinemia. Although such disorders are a relatively uncommon cause of NIHF, they are important because of the high recurrence risk of these mainly autosomal recessive disorders. Careful histology of the placenta, liver, spleen, and bone marrow will often provide a clue that a metabolic storage disorder was present. For many such disorders, testing is available to determine a diagnosis and for prenatal diagnosis in a subsequent pregnancy. Panels of causative storage disorders can be tested for in some laboratories, and this should be considered for cases of NIHF in a structurally normal fetus in which another cause has not been identified, or with cases of recurrence within a family.[76,77]

A number of other syndromes have been associated with NIHF. Many of these are disorders associated with lymphatic dysfunction, such as Noonan and multiple pterygium syndrome, both of which frequently present with cystic hygroma; idiopathic chylothorax, in which a local pleuromediastinal lymph vessel disturbance occurs as the possible pathogenic mechanism; yellow nail syndrome, a dominantly inherited congenital lymphedema syndrome; and congenital pulmonary lymphangiectasia. Familial recurrence in some of these cases suggests a hereditary maldevelopment of lymphatic vessels.[6,14,19,78]

What is the appropriate evaluation when fetal hydrops is detected?

Sonographic identification of the hydropic fetus is not difficult. The diagnostic challenge is to establish the etiology and determine the appropriate therapy (if available) and timing of delivery. It has been reported that the cause of hydrops can be determined in about 60-85% of cases, although this includes postnatal evaluation.[13]

Figure 2 outlines the various steps in the evaluation of the hydropic fetus. It is especially important to rule out potentially treatable conditions, as well as genetic disorders with a risk of recurrence in future pregnancies. Often, the etiology of the hydrops can be determined at the time of diagnosis, since several etiologies are confirmed or excluded based upon ultrasound findings (eg, twin-to-twin transfusion, cardiac arrhythmias, and structural anomalies associated with NIHF).

Management is guided by the presence or absence of additional anomalies. Sonographic evaluation should include a detailed survey for anomalies of the fetus, umbilical cord, and placenta, and estimation of amniotic fluid volume. A fetal echocardiogram should be included, as fetal cardiac anomalies are among the most common causes of NIHF.

In a structurally normal fetus, the first step is to rule out alloimmunization as a cause. The maternal blood type and Rh(D) antigen status are assessed as part of routine prenatal care, along with an indirect Coombs test (an antibody screen) to evaluate for circulating red blood cell antibodies. These results should be reviewed, and if the indirect Coombs test was previously normal, it should be repeated. Maternal blood studies should also include a complete blood cell count with differential and indices, Kleihauer-Betke stain for fetal hemoglobin, and parvovirus B19 serology. Serologic test results for syphilis should be reviewed or repeated, and consideration should be given to acute phase titers for cytomegalovirus and toxoplasmosis.

It is particularly important to perform middle cerebral artery Doppler studies to assess for the presence of fetal anemia, which may be treatable with intravascular transfusion. The fetus with NIHF due to severe anemia will have increased velocity through the middle cerebral artery.[79]

A fetal karyotype, fluorescence in situ hybridization studies, and/or chromosomal microarray analysis should be offered with or without identified sonographic anomalies.[80] This can be performed by amniocentesis or fetal blood sampling; the latter allows direct analysis of fetal hematocrit and hemoglobin if anemia is suspected. Invasive testing also allows testing for lysosomal storage disorders, and polymerase chain reaction studies for parvovirus, toxoplasmosis, and cytomegalovirus infection. Such testing should be performed in a structurally normal fetus in which no other cause has been identified.

An important step in the evaluation of NIHF is to exclude a genetic abnormality. Genetically transmitted disorders account for about one third of cases of NIHF, and include chromosomal abnormalities, hemoglobinopathies, skeletal dysplasias, metabolic storage disorders, and erythrocyte enzymopathies. A complete family history is thus imperative to rule out a known inherited disorder in the family and to assess for consanguinity, which will increase the likelihood of a recessive disorder. Although idiopathic NIHF has a low recurrence risk, the risk for some cases of NIHF may be as high as 25%, making genetic counseling an integral part of the management of any patient with NIHF.

What maternal risks are associated with NIHF?

Women with NIHF may develop mirror syndrome, an uncommon complication in which the mother develops edema that "mirrors" that of her hydropic fetus. Mirror syndrome may represent a form of preeclampsia, and is characterized by edema in approximately 90%, hypertension in 60%, and proteinuria in 40% of cases.[81] As it is uncommon and likely underdiagnosed, the incidence is unclear. Additional associated findings with the syndrome include headache, visual disturbances, oliguria, elevated uric acid, liver function tests, or creatinine levels, low platelets, anemia, and hemodilution.[82] A review of the literature (1956 through 2009) by Braun et al[81] noted that among 56 cases of mirror syndrome, the major maternal morbidity was pulmonary edema, which occurred in 21%. Resolution occurs with either the treatment of the hydrops or with delivery.[81,82]

There have been case reports in which pregnancies with mirror syndrome and various treatable causes of hydrops—secondary to fetal arrhythmia, hydrothorax, parvovirus, and bladder obstruction—have experienced resolution of both hydrops and mirror

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syndrome following treatment.[83-86] The same imbalance of angiogenic and antiangiogenic factors described with severe preeclampsia has also been observed in cases of mirror syndrome, with correction following treatment and resolution of the NIHF.[83,84] However, there are no data regarding the likelihood of resolution or long-term benefits. Given risks of expectant management of severe preeclampsia, it is recommended that this approach be taken only with caution, and that delivery not be delayed if the maternal condition deteriorates. Thus for most cases of NIHF, including all cases without a treatable etiology, development of mirror syndrome necessitates delivery.

What obstetric complications are associated with NIHF?

Polyhydramnios and preterm birth occur frequently with NIHF, with reported incidences as high as 29%[71] and 66%,[87] respectively. If the polyhydramnios is associated with maternal respiratory symptoms, reported management options have included a short course of a prostaglandin inhibitor or serial amnioreduction. Since both treatment modalities lack evidence of benefit and have potential complications, including in utero constriction of the ductus arteriosus, abruption, premature rupture of the membranes, and neonatal complications such as necrotizing enterocolitis and patent ductus arteriosus, they should be used judiciously.[88,89] Tocolytic agents are a consideration <24 weeks if contractions occur secondary to a known inciting event, such as an invasive procedure performed for the diagnosis or management of NIHF.[88] Although in the past preterm delivery has been advocated by some to potentially improve the outcome of NIHF,[7] prematurity is likely to worsen the prognosis. For this reason, we recommend that preterm delivery be undertaken only for obstetric indications.

What is the prognosis of NIHF?

The prognosis of NIHF depends on the underlying etiology, gestational age at detection and delivery, Apgar scores, extent of resuscitation in the delivery room, and whether the newborn requires transport.[90] In one prenatal series, nearly half of those diagnosed <24 weeks had aneuploidy, with extremely poor survival. However, even in the absence of a chromosomal abnormality, survival was <50%.[4] In a recent prenatal series of 71 pregnancies that continued >20 weeks—thereby excluding many with aneuploidy—survival was approximately 50%, and only 25% survived without major morbidities.[12] Among liveborn infants, neonatal mortality with NIHF is

TABLE 2
Therapy for selected etiologies of nonimmune hydrops[21,54,58,59,61,63,64]

Etiology	Therapy	Recommendation
Cardiac tachyarrhythmia, supraventricular tachycardia, atrial flutter, or atrial fibrillation	Maternal transplacental administration of antiarrhythmic medication(s)	Treatment with antiarrhythmic medication unless gestational age is close to term or there is maternal or obstetrical contraindication to therapy
Fetal anemia secondary to parvovirus infection or fetomaternal hemorrhage	Fetal blood sampling followed by intrauterine transfusion	Fetal intrauterine transfusion if anemia is confirmed, unless pregnancy is at an advanced gestational age and risks associated with delivery are considered to be less than those associated with procedure
Fetal hydrothorax, chylothorax, or large pleural effusion associated with bronchopulmonary sequestration	Fetal needle drainage of effusion or placement of thoracoamniotic shunt; if gestational age is advanced, needle drainage prior to delivery in selected cases	Consider drainage of large unilateral pleural effusion(s) resulting in NIHF, or, if gestational age is advanced, consideration of needle drainage prior to delivery
Fetal CPAM	Macrocystic type: fetal needle drainage of effusion or placement of thoracoamniotic shunt; microcystic type: maternal administration of corticosteroids, betamethasone 12.5 mg IM q24 h × 2 doses or dexamethasone 6.25 mg IM q12 h × 4 doses	Consider drainage of large macrocystic CPAM that has resulted in NIHF; if large microcystic CPAM has resulted in NIHF, we suggest that management options include maternal corticosteroid administration
TTTS or TAPS	Laser ablation of placental anastomoses or selective termination	Consideration of fetoscopic laser photocoagulation of placental anastomoses for TTTS or TAPS that has resulted in NIHF <26 wk
Twin-reversed arterial perfusion sequence	Percutaneous radiofrequency ablation	Referral for consideration of percutaneous radiofrequency ablation that has resulted in NIHF

For each of these etiologies, it is recommended that treatment be performed at tertiary care center or center with expertise in relevant therapy.

CPAM, congenital pulmonary airway malformation; *IM*, intramuscular; *NIHF*, nonimmune hydrops fetalis; *TAPS*, twin-anemia polycythemia sequence; *TTTS*, twin-twin transfusion sequence.

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reported to be as high as 60%.[91] With chylothorax as the underlying etiology, the mortality may be as low as 6%; however, when the infant has associated anomalies, almost two-thirds do not survive.[14] Treatable causes of hydrops, such as fetal arrhythmia or infection with parvovirus B19,[92] have a better prognosis. In a large series of newborns admitted to the neonatal intensive care unit, the independent risk factors for death in logistic regression analyses were younger gestational age, low 5-minute Apgar score, and need for high levels of support during the first day after birth (higher levels of inspired oxygen support and greater need for high-frequency ventilation).[14]

Temporal trends suggest that among cases of liveborn infants with NIHF, the associated mortality has not improved over 2 decades. Comparing the mortality among hydropic newborns delivered in 1993 through 2003 vs 2003 through 2009, there was no significant difference in mortality in the 2 time periods, 47% vs 67%, respectively.[91] In addition to the small sample size, an explanation for the lack of improvement in survival over time may be that the more severe cases are now more frequently diagnosed prenatally and referred to tertiary centers, which are more likely to contribute to large series in the literature.

The long-term prognosis for survivors of NIHF also depends upon the underlying etiology. After intrauterine transfusion for hydrops secondary to infection with parvovirus B19, there is potential for delayed psychomotor development and abnormal neurological outcomes.[93] It is unclear if this is because of the hydrops, a direct consequence of the parvovirus infection, from severe anemia, or associated with the transfusion. Finally, fetuses with supraventricular tachycardia may develop Wolff-Parkinson-White syndrome later in life.[94]

Management of NIHF

The cornerstone of counseling and management for this condition is a thorough evaluation for the underlying etiology of the hydrops (Figure 2). Pregnancy management decisions will depend on the etiology, in particular whether there is a treatable cause and the gestational age that NIHF develops or is first identified. Cases generally fall into 1 of 3 categories: those amenable to fetal therapy—which often require urgent treatment or referral to a specialized center; those with a lethal prognosis, for whom pregnancy termination or comfort care are the only options realistic to offer; and cases in which the etiology is idiopathic and the prognosis is likely poor but *uncertain*. Given the poor overall prognosis, pregnancy termination should be offered if NIHF is identified prior to viability. It is important in counseling that the potential for maternal complications with expectant management be anticipated, including mirror syndrome. Serial evaluation of maternal blood pressure is therefore recommended.

What are the fetal therapy options available for NIHF?

Selected etiologies of NIHF for which fetal therapy should be considered are listed in Table 2. Therapy options may include intrauterine transfusion(s) for fetal anemia, medications such as antiarrhythmic agents, drainage of large pleural effusions, corticosteroids for CPAMs, or specialized procedures such as laser coagulation of placental anastomoses for twin-twin transfusion syndrome. The list is not intended to be comprehensive but rather to serve as a

TABLE 3
Society for Maternal-Fetal Medicine recommendations for nonimmune hydrops

Recommendations	Grading of recommendations (Table 4)
• We recommend that initial evaluation of hydrops include an antibody screen (indirect Coombs test) to verify that it is nonimmune, targeted sonography with echocardiography to evaluate for fetal and placental abnormalities, MCA Doppler evaluation for anemia, and fetal karyotype or chromosomal microarray analysis, regardless of whether structural fetal anomalies are identified (Figure 2)	1C Strong recommendation, low-quality evidence
• We recommend that fetal therapy decisions be based on underlying etiology, in particular whether there is a treatable cause (Table 2) and the gestational age that NIHF develops or is first identified	1C Strong recommendation, low-quality evidence
• As prematurity is likely to worsen prognosis, we recommend that preterm delivery be undertaken only for obstetric indications	1C Strong recommendation, low-quality evidence
• We recommend that pregnancies with NIHF due to nonlethal or potentially treatable etiologies be considered candidates for corticosteroid therapy and antepartum surveillance, and that they be delivered at a center that has capability to stabilize and treat critically ill neonates	1C Strong recommendation, low-quality evidence
• We recommend that in most cases, development of mirror syndrome is an indication for delivery	1C Strong recommendation, low-quality evidence

MCA, middle cerebral artery; *NIHF*, nonimmune hydrops fetalis.

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TABLE 4
Grading of Recommendations Assessment, Development, and Evaluation recommendations

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form; further research is unlikely to change our confidence in estimate of benefit and risk	Strong recommendations, can apply to most patients in most circumstances without reservation; clinicians should follow strong recommendation unless clear and compelling rationale for an alternative approach is present
1B Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design; further research (if performed) is likely to have an impact on our confidence in estimate of benefit and risk and may change estimate	Strong recommendation and applies to most patients; clinicians should follow strong recommendation unless clear and compelling rationale for an alternative approach is present
1C Strong recommendation, low-quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws; any estimate of effect is uncertain	Strong recommendation, and applies to most patients; some of evidence base supporting recommendation is, however, of low quality
2A Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form; further research is unlikely to change our confidence in estimate of benefit and risk	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens, some uncertainly in estimates of benefits, risks, and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design; further research (if performed) is likely to have an impact on our confidence in estimate of benefit and risk and may change estimate	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
2C Weak recommendation, low-quality evidence	Uncertainty in estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws; any estimate of effect is uncertain	Very weak recommendation; other alternatives may be equally reasonable
Best practice	A recommendation in which either: (i) there is an enormous amount of indirect evidence that clearly justifies strong recommendation; direct evidence would be challenging, and an inefficient use of time and resources, to bring together and carefully summarize; or (ii) recommendation to contrary would be unethical		

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guideline. With the exception of open fetal surgery, therapy is sometimes offered to pregnancies identified as being at risk for NIHF, with the understanding that the prognosis worsens if hydrops develops.

Counseling for pregnancies with NIHF amenable to fetal therapy should include a discussion of potential risks, benefits, and alternatives that takes into consideration the severity of the underlying condition and the anticipated response to the intervention. If the patient declines therapy or is unable to receive therapy, the prognosis is poor. Given the specialized nature of fetal therapy, patients should receive care from physicians with expertise providing the treatment offered, which in some cases may require evaluation at a specialized center.

When is antepartum fetal surveillance appropriate in NIHF?

Antepartum surveillance is generally used in the setting of maternal or pregnancy complications associated with an increased risk for fetal demise, and when findings from surveillance will assist with delivery decisions. For NIHF, antepartum testing has not been definitively shown to improve perinatal outcomes, and all indications for testing are considered relative.[95] There are no management trials or observational series of the utility of antepartum surveillance in the setting of NIHF upon which to base recommendations. Whether an individual pregnancy with NIHF may benefit from surveillance depends on the etiology of the hydrops, the underlying pathophysiology, and the potential for prenatal or postnatal treatment.

Fetuses with NIH may be candidates for antepartum surveillance if: (1) the underlying etiology of the hydrops is not considered lethal, (2) the pregnancy has reached a viable gestational age, and (3) the findings from surveillance would be used to assist with timing of delivery. In such cases, deterioration of testing results or worsening of the sonographic findings of hydrops might prompt delivery.

Most fetuses with NIHF secondary to an etiology listed in Table 2 are candidates for antepartum surveillance. If fetal therapy is attempted but does not ameliorate the hydrops, the prognosis is significantly worse.[20,61] If the NIHF is idiopathic, counseling about the guarded prognosis should include limitations in available treatment options, but in the absence of a contraindication, antepartum testing may be considered. If there are questions about the postnatal prognosis, consultation with a neonatologist or other pediatric subspecialist may be helpful.

When is the optimal timing of delivery?

There are no management trials of delivery timing in the setting of NIHF upon which to base recommendations. Many hydropic fetuses succumb prior to viability. There is no evidence that elective preterm delivery will improve the outcome. In one retrospective series, preterm birth <34 weeks was a poor prognostic factor.[90] Based on expert opinion, development or worsening of NIHF in a pregnancy that has reached about 34 weeks would seem a reasonable indication for delivery, although given the wide spectrum of etiologies and severity of NIHF, care should be individualized. In the absence of clinical deterioration or other indication for earlier intervention, delivery by 37-38 weeks should be considered. As discussed previously, we recommend delivery in most cases if mirror syndrome develops.

Should corticosteroids be given?

There are no studies that specifically address the utility of antepartum corticosteroid therapy to ameliorate the sequelae of prematurity in the setting of NIHF, and there are similarly no data to suggest that corticosteroid administration is detrimental in pregnancies complicated by hydrops. In 2 retrospective series, neonatal survival was not improved in those who received corticosteroids.[9,96] This was likely due to the overall extremely high morbidity and mortality among infants with NIHF in these cohorts, and that hydrops represents an advanced stage of multiple underlying pathophysiologies. Fetuses with NIHF are at risk for preterm delivery and thus for prematurity-related morbidities that may compound their hemodynamic compromise. Pregnancies with NIHF would reasonably be candidates for antepartum corticosteroid therapy if the gestational age is between 24-34 weeks, if the underlying etiology of the hydrops is not considered lethal, and if intervention is planned on behalf of the fetus should deterioration of the fetal condition occur. If any type of fetal therapy is planned (Table 2) and the gestational age is between 24-34 weeks, corticosteroid administration should be considered.

What is the optimal mode of delivery?

If the fetus is potentially treatable or considered viable, and if the decision to proceed with delivery is based on findings of antepartum surveillance or concern about deterioration of the fetal condition (eg, based on sonographic findings), cesarean delivery may be indicated. Prior to delivery of the hydropic fetus, consideration should be given to whether drainage of a large effusion may improve the efficacy of neonatal resuscitative efforts. Rarely, effusions may be so large as to pose a risk for trauma to the infant during delivery. Depending on the degree of associated effusions and anasarca, consideration should be given to the potential for dystocia at delivery. If a decision has been made not to intervene for fetal indications—to provide comfort care only, vaginal delivery is preferred unless otherwise contraindicated.

Where should delivery occur?

If the NIHF is considered to have an etiology that is potentially amenable to postnatal treatment, or if the etiology of the hydrops is idiopathic, the pregnancy should be delivered at a center with a level-III neonatal intensive-care unit that has the capability to stabilize and treat critically ill neonates. This may require transfer of the pregnant patient prior to delivery.

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RECOMMENDATIONS

Recommendations regarding NIHF are presented in Table 3. The grading scheme classifies recommendations as either strong (grade 1) or weak (grade 2), and classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C). Thus, the recommendations can fall into 1 of the following 6 categories: 1A, 1B, 1C, 2A, 2B, 2C (Table 4).

Quality of evidence

The quality of evidence for each article was evaluated according to the method outlined by the US Preventative Services Task Force:

I	Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or metaanalysis of homogeneous RCTs.
II-1	Well-designed controlled trial without randomization.
II-2	Well-designed cohort or case-control analytic study.
II-3	Multiple time series with or without the intervention; dramatic results from uncontrolled experiment.
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.

This opinion was developed by the Publications Committee of the Society for Maternal–Fetal Medicine (SMFM) with the assistance of Mary E. Norton, MD, Suneet P. Chauhan, MD, and Jodi S. Dashe, MD and was approved by the executive committee of the society on Sept. 29, 2014. Each member of the publications committee (Sean Blackwell, MD [Chair], Mary Norton, MD [Vice Chair], Vincenzo Berghella, MD, Joseph Biggio, MD, Aaron Caughey, MD, Suneet Chauhan, MD, Sabrina Craigo, MD, Jodi Dashe, MD, Brenna Hughes, MD, Jamie Lo, MD, Tracy Manuck, MD, Brian Mercer, MD, Eva Pressman, MD, Anthony Sciscione, DO, Neil Silverman, MD, Alan Tita, MD, and George Wendel, MD) has submitted a conflict of interest disclosure delineating personal, professional, and/or business interests that might be perceived as a real or potential conflict of interest in relation to this publication. ■

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The practice of medicine continues to evolve, and individual circumstances will vary. This opinion reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal—Fetal Medicine.

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