Immune and Non-immune Hydrops

Steven L. Warsof, MD, Kypros H. Nicolaides, MD, and Charles Rodeck, MD

Eastern Virginia Medical School and the Harris–Birthright Research Centre for Fetal Medicine
Norfolk, Virginia
King’s College Hospital Medical School
London, England

Hydrops fetalis (HF) is a state of excessive fluid accumulation into both the extra-vascular compartment and the body cavities, leading to the development of anasarca and ascites, and pleural or pericardial effusions. HF is commonly divided into two major categories. Isoimmune hydrops (I1H) occurs when there is a maternal IgG antibody response to the fetal red blood cell (RBC) antigen leading to hemolysis and anemia. This is most frequently seen, but not limited to, the Rhesus negative (D−), previously sensitized mother carrying a Rhesus positive (D+) fetus. The sensitized mother responds to her fetus by producing anti-D antibodies, which cross the placenta and cause hemolysis of the fetal D+ red blood cells. The second group is referred to as nonimmune hydrops (NIH), hydrops on the basis of a pathologic process other than antigen–antibody RBC hemolysis.

In this article, the causes, characteristics, and treatment of these two disorders are reviewed, and new diagnostic and management approaches are discussed.

Correspondence: Steven L. Warsof, MD, Room 323, Children’s Hospital of King’s Daughters, 800 West Olney Road, Norfolk, VA 23507.

Isoimmune Hydrops

Our understanding of Rhesus isoimmunization has made tremendous strides since the recognition of the Rh blood group by Landsteiner and Weiner in 1940. This has been highlighted by effective prognostication by ΔOD 450 analysis of amniotic fluid, treatment with intrauterine fetal blood transfusions, and then the development of Rh Immune Globulin (RhIG) for the prevention of Rh sensitization.

RhIG Prophylaxis

Although RhIG has become an essential and integral part of obstetric care, it must be remembered that this medication first became licensed in North America in 1968 and did not come into widespread use until the early 1970s.

With the advent of RhIG prophylaxis, the incidence of hemolytic disease in newborns has declined in the United States from 40.5 per 10,000 live births to 14.3 per 10,000 live births between 1970 and 1979. Despite postpartum administration of RhIG, one to two percent of susceptible women still become sensitized.

There are several factors responsible for this. A fetal–maternal hemorrhage (FMH)
resulting in sensitization can occur at any
time during pregnancy. RhIG is therefore
also given at 28 weeks' gestation. The
two-dose RhIG protocol has reduced the in-
cidence of Rh sensitization to between .1%
and .3%. Patients may also become sensi-
tized for failure to use RhIG after first-
or second-trimester losses, amniocen-
tesis, abdominal trauma, or even external
versions. An FMH of greater than 30 cc will occur
in 0.2% of deliveries. This is greater than
the amount of blood hemolyzed by a stan-
ard 300-mcg dose of RhIG. Obstetric
factors associated with large FMH include
cesarean deliveries, multiple gestations,
manual removal of the placenta, and still-
births. In these cases, the FMH should be
quantified and additional RhIG given if
indicated.

Other rare causes of Rh sensitization
include transfusion of mismatched blood
or patient noncompliance on religious
grounds, such as with Jehovah's Witnesses.
In addition, a small but increasing number of
women are cared for outside the medical
system and do not receive RhIG.

Finally, hemolytic isoimmune disease
may occur in Rh-positive patients because
of incompatibility to other antigens. RhIG
is specific for the D antigen and cannot
prevent sensitization caused by any other
antigen. Of most concern are the K antigen
in the Kell system, Fy\textsuperscript{a} antigen in the Duffy
system, and the C and E antigens of the
Rhesus system.\textsuperscript{5}

**Rh Antibody Screening**

Indirect Coombs testing is a widely avail-
able screening test that can be used to de-
termine the presence of maternal anti-
body. If positive, then the antibody must
be identified and quantified. Once identi-
fied, the father of the baby should be tested
for the presence of this antigen. If the
father has the antigen, then the fetus is at
risk. If the quantity of anti-D antibody is
above a "critical value" usually considered
4 iu/ml or a titer of greater than 1:8, then
the amount of hemolysis must be deter-
mined.\textsuperscript{6} This "critical value" has been
determined only for the anti-D antibody.

**Prediction of Fetal Hemolysis**

**Amniotic Fluid Optical Density**

The amount of hemolysis can be predicted
by spectrophotometric analysis for biliru-
bin pigments in amniotic fluid. This is
done by measurement of optical density
differences at 450-nm wavelength. The
AOD 450 is then plotted on the Liley curve
for prognosis.\textsuperscript{7} Serial testing is frequently
necessary to determine trends.

Liley's curve originally ranged from 27
weeks to term and contained three zones.
With the introduction of diagnostic ul-
trasound and ultrasound-guided procedures
in the late 1970s, there was a recognition
that fetuses may benefit from treatment
before 27 weeks. The Liley curves were
then extrapolated linearly back into the
second trimester.\textsuperscript{8,9}

**Ultrasonography**

Sensitization can be suspected ultrasono-
graphically by the presence of polyhy-
dramnios and hyperplacentosis. The ap-
pearance of hydrothorax, pericardial
effusions, and anasarca are diagnostic of
end-stage hydrops.

Some investigators have felt that ultras-
ound may be diagnostic of prehydropic
severe disease in the second trimester.\textsuperscript{10}
Ultrasonic parameters, including placental
thickness, umbilical vein diameter, abdomi-
nal circumference, head : abdomen cir-
cumference ratios, and intraperitoneal vol-
umes, were determined and compared to
severity of disease as judged by fetal cord
hemoglobin levels. In the absence of fetal
hydrops, none of these ultrasonic param-
eters could reliably distinguish mild from
severe disease in the second trimester.\textsuperscript{11}
Fetal Blood Sampling

Direct access to pure fetal blood enables the operator to determine the fetal hemoglobin concentration and to assess the severity of hemolytic disease. Rapid fetal karyotyping and blood typing can also be accomplished. The fetoscopic technique has been described for both fetal blood sampling and treatment of Rhesus isoimmunization. The technique of ultrasonic-guided percutaneous umbilical cord blood sampling without fetoscopy has also been recently described for both diagnosis and fetal transfusion.

In a study of 153 fetal blood samples taken between 16 and 25 weeks' gestation in pregnancies not affected by Rhesus isoimmunization, the hemoglobin concentration was noted to be constant with respect to gestational age at 12.14 g/dl (SD = 1.2 g/dl). With this normative data, severity of disease and the need for transfusion could be accurately determined.

The diagnostic accuracy of extrapolated Liley curves in the second trimester has recently been compared with actual fetal hematocrits. In a study involving 59 Rhesus isoimmunized pregnancies between 18 and 25 weeks' gestation, amniotic fluid was obtained for ∆OD 450 analysis. Fetal blood sampling was also performed by fetoscopically guided umbilical vessel puncture. Thirty-one of 59 fetuses were judged to have very severe disease by cord hemoglobins of <6 g/dl. Fourteen of these 31 also had ultrasonic evidence of hydrops. Only 10/31 (32%), however, had OD 450 in the extrapolated zone 3. This yielded a 68% false-negative rate. Table 1 gives details of this analysis. From these results, it can be seen that the extrapolated Liley curve in the second trimester is a poor predictor of the severity of isoimmunization.

Fetal Blood Transfusion

In the presence of severe disease in the previable fetus, intrauterine transfusion should be performed. Severe disease can be determined in the second trimester, preferably by direct fetal blood sampling or by the ultrasonic diagnosis of hydrops. If fetal blood sampling is not available, ∆OD values in zone 3 in the late second and third trimester or rising serial values into zone 3 should also be treated as severe disease. Antepartum transfusion should be performed before 30–32 weeks. After that time, delivery must be considered as an alternative to transfusion.

Intrapertitoneal Transfusion

The technique of in-utero intraperitoneal transfusion (IPT) was first described by Liley in 1963. It has now been modified

<table>
<thead>
<tr>
<th>TABLE 1. Accuracy of Amniotic Fluid ∆OD 450 Values in Predicting Severity of Isoimmunization Between 18 and 25 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetal Hemoglobin Concentration</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>All Fetuses</strong></td>
</tr>
<tr>
<td>Lily zone 1</td>
</tr>
<tr>
<td>Lily zone 2a</td>
</tr>
<tr>
<td>Lily zone 2b</td>
</tr>
<tr>
<td>Lily zone 3</td>
</tr>
</tbody>
</table>

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931610/ on 11/08/2018
over the past 20 years from a blind procedure using x-ray and fluoroscopic guidance to an ultrasound-guided technique. Intraoperative real-time ultrasound guides needle placement and allows the operator to visualize the fetus throughout the entire procedure.

The IPT is the most commonly used technique for treatment of severe isoimmunization. The reader is referred to several review articles for details on methodology and technique.\(^8\)\(^9\)\(^18\)\(^19\) The success rate of this technique is variable, with experience in North America more optimistic than that reported in the United Kingdom.\(^20\)\(^21\) It is clear that the best outcome is obtained by an experienced team doing IPT on a regular basis. Severity of disease, previous pregnancy outcome, the presence of hydrops, and the gestational age at time of first transfusion are the most important prognostic factors.

**Intravascular Transfusion**

Under local anesthesia and sedation to reduce maternal and fetal movements and employing full aseptic technique, the fetoscope, a 1.7-mm diameter endoscope, is introduced transabdominally into the amniotic cavity. Under direct vision, an umbilical cord artery is punctured, and a pure fetal blood sample is obtained for hematologic and biochemical analysis. With the tip of the needle remaining in the lumen of the vessel, fresh Rhesus negative packed RBCs compatible with the mother are infused at a rate of 1–3 ml per minute. An umbilical artery is preferred to the vein because it will carry the transfused blood to the placenta where oxygenation, addition of base, and mixing will occur before entry into the fetus. Furthermore, the danger of thrombotic occlusion of the single umbilical vein is likely to be more serious than if thrombosis occurred in one of the two umbilical arteries. The quantity of blood transfused is determined by consideration of the estimated fetoplacental blood volume, the pretransfusion hematocrit, and the hematocrit of the donor blood. Intravascular transfusions (IVTs) can be started as early as 18 weeks’ gestation and repeated at 1–3 week intervals up to 30–32 weeks. Close monitoring of the pregnancy, including fetal activity monitoring, frequent non-stress tests, and ultrasound, are essential. Delivery is accomplished at sign of any compromise or at 32–34 weeks. The precise timing of delivery must be determined on an individual basis with close neonatal collaboration.

Because of aggressive antenatal transfusion of these fetuses reversing hydrops and severe anemia, the neonatal course is often surprisingly benign, especially in view of the nature and severity of the isoimmunization at their presentation.\(^12\) The neonatal RBC volume has been almost totally replaced by the transfused cells, and frequently only simple transfusions are required after delivery.

Using this approach for the management of 50 severely Rhesus isoimmunized pregnancies, including 23 with hydrops, referred before 25 weeks’ gestation, the overall survival rate achieved was 84%; 25 of the 27 (92%) nonhydropic and 17 of the 23 (71%) hydropic ones survived. Reversal of hydrops was commonly seen with successful transfusions.\(^12\)

In view of the severity of isoimmunization in this series as judged by 46% with hydrops before 25 weeks, the degree of anemia present at first transfusion, and the past obstetric history of these patients, the survival rates are superior to those anticipated by the more traditional IPT approach.

The ability to perform the IVT 4–6 weeks earlier than the IPT is a distinct advantage of this technique. The high survival rates achieved for severely affected and hydropic fetuses emphasize the importance of early correction of anemia and sharply contrast previous reports with IPT. Fetoscopically directed IVT allows for
exact quantification of pre- and post-transfusion hematocrits to judge the severity of the disease, the amount of blood needed, and the adequacy of the transfusion. Furthermore, they remove the problem of uncertain and delayed absorption through the peritoneum, especially in the presence of hydrops, by placing the blood directly into the fetal vascular compartment.

**Expectant Management**

As an alternative to late transfusion therapy (>30 weeks), a conservative approach to managing pregnancies in or near Liley zone 3 with serial nonstress tests and ultrasound scans has been described. Delivery would be accomplished at the earliest signs of ascites or for a nonreactive NST. In this way, the hazard of transfusions was avoided in the majority of patients in this series. This approach would not be appropriate for severely sensitized pregnancies presenting in the second trimester.

**Medical Treatment**

Other medical techniques have been advocated for the treatment of isoimmunization. These include intensive plasmapheresis to reduce circulating antibody levels, oral desensitization with ingestion of Rhesus positive RBC membranes, and “neutralization” by injection of a Rhesus positive hapten. In addition, prevention of hemolysis has been attempted with corticosteroids and promethazine. The former was to inhibit macrophage binding to stabilize antibody-coated RBCs and to inhibit their destruction by phagocytosis in the reticuloendothelial system. These techniques have been of limited value in our practice.

**Pathophysiology**

Aside from the important information of fetal hemoglobin concentration, fetal blood sampling has made the determination of other hematologic values possible in severely Rhesus sensitized pregnancies. When the fetal hemoglobin fell below 4 g/dl, then marked reticulocytosis, leukocytosis, and thrombocytopenia occurred in the deteriorating fetal cardiovascular system.

Fetal plasma protein and albumin have also recently been measured in a series of 17 fetuses with severe Rhesus isoimmunization, seven of whom had hydrops at time of blood sampling. Total protein was below -2 SD in all hydropic fetuses and 6 of 10 nonhydropic fetuses. Hypoalbuminemia was also noted in 6 of 7 hydropic and 2 nonhydropic fetuses.

Although the precise pathophysiology of the development of hydrops in isoimmunization remains unclear, severe chronic anemia acting through tissue hypoxia is most likely the initiating factor. This process is worsened by hypoproteinemia and hypoalbuminemia. Diffuse extramedullary hematopoiesis leads to distortion of the hepatic parenchyma. This causes increasing portal and umbilical hypertension until a loss of vascular competency leads to the appearance of hydrops.

Figure 1 outlines the recommended management of isoimmunized pregnancies modified by the ability to obtain fetal blood samples and to perform IVTs.

**Nonimmune Hydrops**

Hydrops not associated with erythroblastosis was first described in 1943 by Potter. Until recently it was a very rare disorder. However, with the introduction of Rh immune globulin and subsequent dramatic fall in HF from isoimmunization, the percentage of hydropic patients from other causes has increased. Furthermore, the widespread use of ultrasonic fetal evaluation is detecting many cases of NIH that would have previously presented as unexplained stillbirths. At Eastern Virginia Medical School, the ratio of NIH to IIH is 9:1.
FIG. 1. Management of isoimmunized pregnancies.
Etiology
The causes of NIH are many and can be attributed to problems of any fetal system (Fig. 2). Most recent series, however, report that more than 50% of cases must be classified as idiopathic or of unknown cause. In a recent series, when primary diagnoses were aggressively pursued, congenital heart disease or arrhythmias (20%) were the most common causes in Caucasians, followed by chromosomal abnormalities (16%). Alpha thalassemia was most commonly seen in the Asian population.28

Diagnosis
The usual presentation of NIH is polyhydramnios or decreased fetal movement, which leads to an ultrasound evaluation and discovery of NIH. Frequently, the diagnosis is made by ultrasound requested for routine or nonrelated indications.

A. Fetal
1. Hematologic
   Homozygous alpha thalassemia
   Chronic fetomaternal transfusion
   Twin-to-twin transfusion
   Multiple gestation with parasitic fetus
2. Cardiovascular
   Severe congenital heart disease (ASD, VSD, hypoplastic left heart, pulmonary valve insufficiency, Ebstein's anomaly, subaortic stenosis)
   Premature closure of foramen ovale
   Myocarditis
   Large A-V malformation
   Tachyarrhythmias: atrial flutter, SVT
   Bradyarrhythmias: heart block
   Fibroelastosis
3. Chromosomal
   Trisomy 21
   Turner's syndrome 45X0
   Other trisomies
   Triploidy
   Mosaicism
4. Pulmonary
   Cystic adenomatoid malformation of lung
   Pulmonary lymphangiectasia
   Pulmonary hypoplasia
   Congenital chylothorax

5. Renal
   Congenital nephrosis
   Renal vein thrombosis
   Posterior urethral valves
   Spontaneous bladder perforation
6. Intrauterine Infections
   Syphilis
   Toxoplasmosis
   Cytomegalovirus
   Leptospirosis
   Chagas disease
   Congenital hepatitis
   Herpes simplex
7. Congenital Anomalies
   Achondroplasia
   Thanatophoric dwarfism
   Sacrococcygeal teratoma
8. Miscellaneous
   Meconium peritonitis
   Fetal neuroblastomatosis
   Tuberous sclerosis
   Small-bowel volvulus

B. Placental
   Umbilical vein thrombosis
   Chorioangioma
   True cord knots
C. Maternal Disease
   Diabetes mellitus
   Toxemia
   Severe anemia
D. Idiopathic

FIG. 2. Etiology of nonimmune hydrops.
When hydrops is discovered, it is initially important to differentiate NIH from I IH. This is done by indirect Coombs antibody screen. If this is negative, then a systematic approach investigating all the potential causes of NIH is necessary in order to determine the cause (Fig. 3). Of utmost importance is tertiary-level ultrasound in order to evaluate each fetal system. This must include thorough structural and functional evaluation of the fetal heart. Although it is impossible to differentiate between NIH and I IH by ultrasound alone, our experience reveals that NIH is frequently associated with the presence of severe anasarca, ascites, and hydrothorax at first presentation in midgestation. This is usually only a very late appearance in isoimmunization.

Fetal Blood Sampling

Fetoscopy and direct fetal blood sampling where available are valuable in the speedy evaluation of NIH. Rather than obtain indirect information about the fetus from maternal serology or amniotic fluid, fetal blood sampling gives direct access to the status of the fetus. Karyotyping can also be done in 2–4 days from fetal lymphocytes rather than 2–4 weeks from cultured amniocytes, and specific IgMs can be measured in fetal blood.29

Treatment

Management must be individualized. Close follow-up with repeat ultrasonic evaluations for the progress of disease is critical. Fetal movements and cardiocotography play a critical role. Medical and surgical therapies may be indicated in specific instances. If an arrhythmia is discovered, then it must be identified and converted. Digoxin, quinidine, and procaainamide have all been used. Since arrhythmias can be sporadic, an argument can be made for using digoxin in cases of severe NIH of unknown cause when delivery is impossible because of prematurity. Furosemide may be helpful in mobilizing excessive third-

A. Hematologic
1. CBC—if anemic, electrophoresis, sickledex, G6PD
2. VDRL
3. TORCH titers
4. Blood type and Rh
5. Antibody screen
6. SMAC-23 including LFTs, bilirubin, BUN, creatinine, electrolytes, albumin, and protein
7. Kleihauer-Betke test
8. Maternal serum alpha fetoprotein
9. Parental HLA type (if recurrent or idiopathic)

B. Urologic
1. Urine analysis
2. CMV culture

C. Ultrasound
1. Full growth study
2. Amniotic fluid volume, placental thickness
3. Morphologic survey for anomalies
4. Cardiac evaluation: rhythm and chamber size
5. Major vessel sizes
6. Skin thickness
7. Internal free fluid

D. Amniotic Fluid or Fetal Blood Sample
1. Karyotype
2. TORCH titers
3. Specific infection IgMs if suspicious
4. Viral cultures
5. AOD 450
6. Alpha fetoprotein
7. Fetal blood film and indices
8. Fetal plasma albumin and total protein

E. At Delivery
1. Karyotype if not done
2. Autopsy
3. Viral studies
4. Photographs
5. X rays

FIG. 3. Workup of nonimmune hydrops.
space fluid in the fetus. Ultrasound-guided para- or thoracocentesis may be indicated, although the benefits of this intervention remain unclear. In cases in which fetal blood sampling has revealed hypoalbuminemia, fetal intravascular albumin infusions have been performed but appear of only limited benefit. Preterm delivery may be indicated in some cases, although adding problems of severe prematurity to a hydropic newborn is not beneficial.

Prognosis

Despite recent advances, the fetal prognosis in NIH is generally poor, especially when no cause can be determined. At King's College Hospital, London, in a recent series of 30 pregnancies from which fetal arrhythmias were excluded, survival was only 10%. This poor survival rate has also been demonstrated in other series with perinatal losses reported from 75–90%. Survival is most common in cases in which hydrops is related to a cardiac arrhythmia, particularly when this is able to be converted to normal rhythm and the hydrops clears.

Recurrence of idiopathic NIH is fortunately quite rare. In those cases in which a cause is determined, recurrence risk is that of the disease. With increasing surveillance, more recurrences have been noted, and in one case there were three. Clearly, subsequent pregnancies must be followed closely, and if a chromosomal abnormality was noted in the proband, then karyotyping should be offered. Serial ultrasound evaluations are important to follow fetal development.

As mentioned earlier, despite complete workup, approximately one-half the cases of NIH remain idiopathic. In this group of patients, and in those with recurrent idiopathic hydrops, parental HLA typing may be important. In our preliminary investigations, we have discovered two cases of idiopathic NIH in which the parents have similar HLA alleles. It can be theorized that in these instances, common fetal and maternal HLA haplotypes derange the normal immunologic responses, and in these instances NIH may be secondary to an abnormal maternal immunologic response to her fetus.

Conclusion

Fetal hydrops is associated with two distinct pathophysiologic situations. IIH is a well-understood disorder, which because of medical advances and prophylactic therapy has become a rare entity. NIH remains a poorly understood disease with a poor prognosis. The two disorders can be differentiated by the indirect Coombs test. In both cases, ultrasonic antenatal evaluation plays a critical role in diagnosis, prognosis, and management.

Fetal blood sampling either by ultrasound guidance or by the combined ultrasound and fetoscopic approach has recently been used in these disorders. With NIH, access to fetal blood has been effective in rapid diagnosis of the cause of NIH. It has thus far been of limited value in treating the disorder.

With isoimmunization, fetal blood sampling and the subsequent ability to perform direct intravascular transfusion have brought new hope to pregnancies affected with early severe isoimmunization, where the standard technique of intraperitoneal transfusions was of limited value.

References

5. Weinstein L. Irregular antibodies causing
11. Nicolaides KH, Rodeck CH. Failure of six ultrasonographic parameters to predict the severity of fetal anemia in Rh isoimmunization. Submitted for publication.
16. Nicolaides KH, Rodeck CH, Kemp JR, Mi-bashan RS. Have Liley charts outlived their usefulness? Submitted for publication.