DIAGNOSIS AND MANAGEMENT OF FETAL HYDROPS

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Objectives

- Understand how to make the diagnosis of fetal hydrops
- Recognize the difference between immune and non-immune hydrops
- Delineate the causes of immune and non-immune hydrops
- Develop a clear and rational plan for the management of fetal hydrops
Hydrops fetalis is Latin for “edema of fetus”

First reported by Ballantyne in 1892, although it has been recognized for >300 years

It remains an important cause of stillbirth and neonatal death in developed countries

- Complicates <0.5% of all pregnancies
- Prognosis depends on cause, severity, and gestational age
- Overall perinatal mortality rate exceeds 50%
Hydrops fetalis is an ultrasound diagnosis.

Refers to an abnormal accumulation of fluid in two or more extravascular compartments of the fetus:
- Ascites
- Pleural effusion
- Pericardial effusion (>2mm)
- Subcutaneous edema (soft tissue thickness >5mm, may be isolated or generalized ‘anasarca’)
Polyhydramnios is seen in 50-75% of cases

- But is not part of the diagnostic criteria

Placental edema / thickening (>5-6cm over its entire extent) may be seen on ultrasound

- It is also not part of the diagnostic criteria
- Often a late finding
- Exclude ‘mirror syndrome’ (secondary preeclampsia)

Fetuses often have hepatosplenomegaly

- May represent extramedullary hematopoiesis
A transverse section through the fetal head: the halo around the head is due to skin edema

A transverse section through fetal chest: bilateral pleural effusions + skin edema are evident
Ultrasound (2)

A transverse section through the fetal abdomen: ascites + skin edema are evident

A longitudinal section through the fetal body: ascites, pleural effusion + skin edema are evident
Ultrasound (3)

A transverse section through the fetal abdomen: ascites + floating bowel are evident

A transverse view through the uterus: a thickened anterior placenta

Depth = 8.8 cm
Ultrasound (4)

A sagittal section at 13 weeks of gestation showing **anasarca** + **cystic hygroma**

Neonate with evidence of **generalized fetal hydrops**
Isolated collection of fluid in one extrascular compartment (such as isolated pleural effusion, ascites) should not be confused with hydrops.

Other sources of confusion include:

- Thickened fetal scalp due to fetal hair
- Subcutaneous fat
- Cystic hygroma
- Thickened folded skin (“crocodile skin”)
- Physiologic pericardial effusion (<2mm)
Skin thickening and folding ("crocodile skin") that can be confused with skin edema

Fetal hair can form an irregular halo around the head that can be confused with scalp edema
Immune hydrops (10%)
- Also known as erythroblastosis fetalis or hemolytic disease
- Screening: blood type/antibody screening recommended for all women at first prenatal visit (1% will have +ve antibody)

Non-immune hydrops (90%)
- Refers to hydrops fetalis without an immune etiology
- Since the introduction of anti-Rh(D) immunoglobulin, non-immune hydrops is the most common cause of hydrops fetalis (~1 in 2000 live births)

Cause cannot be distinguished by ultrasound
Severity can be distinguished by ultrasound

- Mild / moderate hydrops can be managed expectantly
- Active intervention is needed for severe hydrops

Classification of Severity of Hydrops Fetalis

<table>
<thead>
<tr>
<th>Classification of Severity</th>
<th>Mild (50%)</th>
<th>Moderate (25%)</th>
<th>Severe (25%)</th>
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<tbody>
<tr>
<td>Mild (50%)</td>
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<tr>
<td>- No treatment is required</td>
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<tr>
<td>- Mild anemia at birth</td>
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<td>- hemoglobin &gt;10 g/dL</td>
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<td>- serum indirect bilirubin &lt;15-20 mg/dL</td>
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<td>Moderate (25%)</td>
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<td>- So long as the fetus is in utero, products of red blood cell destruction (bilirubin) are transferred across the placenta and metabolized by the mother</td>
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<td>Severe anemia with erythropoiesis from liver, spleen, and other extramedullary sites</td>
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<td>- After birth, fetuses are at risk of developing kernicterus (bilirubin encephalopathy) with a 90% mortality. To avoid accumulation of indirect bilirubin, phototherapy may be needed.</td>
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<td>- Moderate anemia is usually present at birth</td>
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<td></td>
<td>Boggy edematous placenta</td>
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<tr>
<td>Severe (25%)</td>
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<tr>
<td>Maternal complications include:</td>
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<td></td>
<td>Pleural effusions</td>
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<tr>
<td>- polyhydramnios (50-70%)</td>
<td></td>
<td></td>
<td>Ascites, hepatosplenomegaly</td>
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<tr>
<td>- anemia</td>
<td></td>
<td></td>
<td>Anasarca (whole body edema)</td>
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<tr>
<td>- preeclampsia (35-50%)</td>
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<td>- postpartum hemorrhage</td>
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<td>- retained placenta</td>
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Norwitz ER, Schorge JO. Obstetrics & Gynecology at a Glance, 4th edition
Immune hydrops

Caused by antibodies against proteins on fetal erythrocytes not present on maternal cells

- IgG cross the placenta and destroy fetal erythrocytes leading to fetal anemia and high-output cardiac failure
- Hydrops is assoc with fetal hematocrit <12% (normal 50%)
- Rh(D) is most antigenic protein (~30% of immune hydrops)
- Other antigens which can cause severe immune hydrops include Kell (“Kell kills”), Rh(E), Rh(c), Duffy (“Duffy dies”)
- Antigens causing less severe hydrops include ABO, Rh(e), Rh(C), Fya, Ce, k, s
- Lewisa,b causes mild anemia but not hydrops (because IgM)
Rh antigen complex (D, E, e, C, c, G) is only found on primate erythrocytes

- Unlike ABO, which is found also on bacteria
- Rh antigens are evident by 38 days of intrauterine life

Mutation in the Rh(D) gene on chromosome 1 results in lack of expression of D antigen on circulating erythrocytes = Rh(D)-negative

- Arose in Basque region of Spain, which explains the racial differences (Caucasians 15%; African-Americans 8%; Africans 4%; Asians 2%; Native Americans 1%)
Isoimmunization can be caused by as little as 0.25 mL of Rh-positive blood

- Antibody response seen in 5-15 weeks; initially IgM

Risk factors for Rh isoimmunization

- Mismatched blood transfusion (95% sensitization rate)
- Ectopic pregnancy (<1%)
- Abortion (3-6%)
- Amniocentesis (1-3%)
- Pregnancy (16-18% sensitization rate following normal pregnancy without anti-D IgG; 1.5% with anti-D IgG at delivery; 0.13% with anti-D IgG at delivery + 28 weeks)
Passive immunization with anti-Rh(D) IgG can destroy fetal erythrocytes before they evoke a maternal immune response

- Should be given within 72 hours of potential exposure (vaginal bleeding, delivery) and empirically at 28 weeks
- 300mg (U.S.) or 500IU (U.K.) IM will cover up to 30mL fetal whole blood or 15mL fetal red cells

There is no passive immunization for other erythrocyte antigens
Screening in pregnancy

- Check antibody titers every 2-4 weeks
- Critical cutoff values vary from 1:8 to 1:32 (we use 1:16)

- Fetal Rh status can be determined by noninvasive (cfDNA) or invasive testing (amnio, PUBS)

Norwitz ER, Schorge JO. Obstetrics & Gynecology at a Glance, 4th edition
Non-immune hydrops

- Refers to hydrops without an immune etiology

- Etiology is varied; major causes include …
  - Idiopathic (no known cause) (50-60%)
  - Cardiac abnormalities (20-35%) including congenital dysrhythmias and structural cardiac anomalies
  - Chromosomal anomalies (15%) such as Turner syndrome
  - Hematological aberrations (10%) such as α-thalassemia, anemia
  - Infections (such as syphilis, toxoplasmosis, parvovirus B19)
  - Other causes (fetal structural anomalies, twin-to-twin transfusion syndrome, vascular malformations, placental anomalies, congenital metabolic disorders)
Management

- Confirm the diagnosis by ultrasound

- Subsequent management depends on the cause, severity, and gestational age

  ➔ Search for a potentially reversible / treatable cause
    - Take a detailed history (e.g., of recent maternal infection)
    - Check serologic screening (blood type / antibody screen)
    - Check serology for toxoplasmosis, rubella, CMV, herpes, parvovirus B19
    - Kleihauer-Betke test (an acid elution test for fetal-maternal hemorrhage)
    - Sonographic fetal survey
    - Consider fetal karyotype
    - Fetal anemia

- Pregnancy termination may be an option
Spectral analysis of AF

- Fetal hemolysis releases bile pigment into AF that can be measured as change in optical density at wavelength 450nm ($\Delta OD_{450}$)
  - Only useful if cause of anemia is hemolysis (not for Kell)

- Traditionally, serial amniotic fluid $\Delta OD_{450}$ measurements were plotted against gestational age to guide management
  - Serial amnio every 10-14 days once titers are elevated
  - Plot $\Delta OD_{450}$ on Liley or Queenan curves
If the $\Delta OD_{450}$ rises into the upper 80% of zone 2 or into zone 3 of the Liley curve, prompt intervention is indicated.

Scott F, Chan FY. *Prenat Diagn* 1998; 18:1143-8
Physics of Doppler

\[ f_D = 2f_0 v \cos \theta / c \]

- \( f_D \) = Doppler shift
- \( f_0 \) = frequency of transmitted ultrasound
- \( v \) = velocity of flow
- \( \theta \) = angle of insonation
- \( c \) = velocity of sound in tissue
Basic principles

**Doppler Indices**

- **RI** = \((S - D) / S\) (Pourcelot, 1974)
- **PI** = \((S - D) / A\) (Gosling, 1976)
- **S/D Ratio** = \(S/D\) (Stuart & Drumm, 1980)

- **S** = systolic peak (max. velocity)
- **D** = end diastolic flow
- **Vm** = mean velocity
- **A** = Temporal average frequency over 1 cardiac cycle
Middle cerebral artery (MCA)

- Transverse view of the BPD
- Move towards the base of the skull at the level of the lesser wing of the sphenoid bone
- Circle of Willis
- Apply minimal pressure to the abdomen with the transducer
- Fetal head compression is associated with alterations of intracranial arterial waveforms
MCA and fetal anemia

Normal MCA Peak Systolic Velocity (PSV) for gestational age

Elevated MCA PSV for gestational age suggestive of fetal anemia (due to decreased viscosity + increased blood flow or “brain sparing”)
(111 isoimmunized pregnancies vs 265 normal pregnancies; MCA PSV increased with anemia; sensitivity of MCA PSV >1.5 MoM to detect moderate or severe anemia was 100% with a false-positive rate of 12%, PPV 65%, NPV 100%)
MCA PSV and fetal anemia

- False-positive rate 10-15%
- Start as early as 16-18 weeks
- Perform weekly
- Not reliable after 35 weeks
- MCA PSV >1.5 MoM → proceed with percutaneous umbilical blood sampling (PUBS) ± IUT

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**Table 3. Expected Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery as a Function of Gestational Age.**

<table>
<thead>
<tr>
<th>WEEK OF GESTATION</th>
<th>MULTIPLES OF THE MEDIAN</th>
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<tr>
<td></td>
<td>1.00 (MEDIAN)</td>
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<tr>
<td></td>
<td>cm/sec</td>
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<tr>
<td>18</td>
<td>23.2</td>
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<td>20</td>
<td>25.5</td>
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<tr>
<td>22</td>
<td>27.9</td>
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<td>24</td>
<td>30.7</td>
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<td>26</td>
<td>33.6</td>
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<tr>
<td>28</td>
<td>36.9</td>
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<tr>
<td>30</td>
<td>40.5</td>
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<tr>
<td>32</td>
<td>44.4</td>
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<tr>
<td>34</td>
<td>48.7</td>
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<tr>
<td>36</td>
<td>53.5</td>
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<tr>
<td>38</td>
<td>58.7</td>
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<tr>
<td>40</td>
<td>64.4</td>
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PUBS ± intrauterine transfusion

- Check baseline maternal MCV
- Check cord blood MCV + HCT
- Paralyze fetus (vecuronium + fentanyl)
- If fetal HCT <30%, transfuse O- / CMV- / irradiated blood with HCT 80% at 1 mL/min (up to 4x initial HCT or HCT of 25% if hydropic)

Complications of PUBS

- Procedure-related fetal loss (1-3%)
- Risk assoc with any invasive procedure (1-20%)
  - Bleeding
  - Infection
  - Rupture of membranes
  - Labor
  - Isoimmunization
  - Non-reassuring fetal testing requiring emergent delivery

Moise KJ Jr, Argoti PS. *Obstet Gynecol* 2012; 120:1132-9
Overall survival is **92-94% without hydrops** and **70-78% with a history of hydrops**


van Klink JM, et al. *Early Hum Dev* 2011; 87:589-93

**Long-term morbidity includes** …

- Cerebral palsy / neurodevelopmental delay 4-10%
- Permanent hearing loss 10-20%


van Klink JM, et al. *Early Hum Dev* 2011; 87:589-93

Obstetric management

- **Timing of subsequent PUBS ± IUT varies**
  - Typically 10-14 days
  - MCA PSV less reliable after IUT (use cut-off >1.32 MoM)

- **Antenatal steroids / capacity to perform emergency cesarean if fetus viable**

- **Last IUT at 34-35 weeks’ gestation**

  - Moise KJ Jr, Argoti PS. *Obstet Gynecol* 2012; 120:1132-9
Consider alternative therapies in select cases

- **Erythropoietin** either antepartum or in neonatal period
  

- **Plasmapharesis**
  

- **Intravenous immunoglobulin (IVIG)** 1g/kg weekly to prevent anemia, decrease severity of anemia, and/or delay the development of anemia until IUT can be performed
  
  Fox C, et al. *Fetal Diagn Ther* 2008; 23:159-63
Consider fetal testing weekly > 32 weeks

Delivery at 37-38 weeks’ gestation

➤ Cesarean for routine obstetric indications only

Close neonatal follow-up needed

➤ 10% of infants need postnatal transfusion for persistent ‘hyporegenerative’ anemia even if in Liley Curve Zone I

Moise KJ Jr, Argoti PS. Obstet Gynecol 2012; 120:1132-9
Conclusions

- Confirm **diagnosis by ultrasound**

- **Assess risk for fetal anemia**
  - Type of antibody
  - Paternal antigen status
  - Determine fetal antigen status (noninvasive vs invasive tests)
  - Antibody titer

- **Monitor for anemia by MCA Dopplers**

- **Transfuse as needed**

- **Optimal timing of delivery**