THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

# Fetal Anemia

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# Objectives

- Define Fetal Anemia
- Examine Causes/Etiologies
- Describe Diagnostic Assessment and Work up
- Potential Fetal Therapies and Newborn Outcomes

# Fetal Anemia

- Defined using either the hemoglobin (Hgb) or Hematocrit (Hct) that is 2 standard deviations (SD) below the mean.
- Severity of Anemia is based on concentrations expressed as multiples of the median (MoM's).
  - Mild (MoM 0.83-0.65)
  - Moderate (MoM 0.64-0.55)
  - Severe (MoM <0.54)
- Hydrops develops when fetal Hgb <5%
- Classic definition used in literature - Fetal Hct <30%

# Causes of Fetal Anemia

- Maternal Alloimmunization
  - Blood transfusion
  - Fetal-Maternal hemorrhage
    - Delivery – Usually C/S or instrumented delivery
    - Trauma/Abruption
    - SAB/induced abortion
    - Ectopic
    - Invasive procedures (amniocentesis or PUBS)
- Rh(D)
- Parvo B19 Virus infection (other viruses, TORCH)
- TTTS/TAPS (Monochorionic twins)
- Inherited Blood Disorders

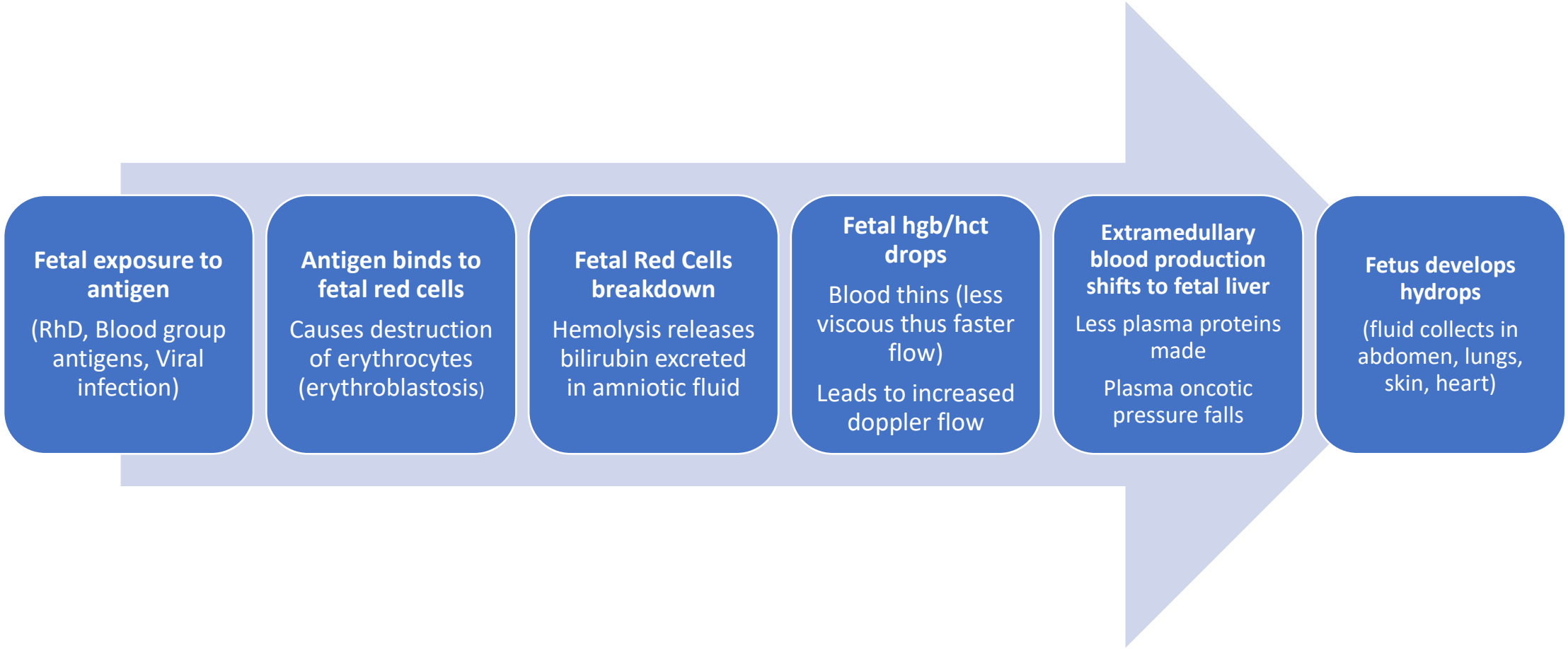
# Diagnosis of Fetal Anemia

- Based on the suspected etiology of anemia
- Red Cell Alloimmunization
  - Determine red cell antibody by maternal screening
    - Determine partner's antigen status
    - Determine fetal antigen status
      - Direct amniocytes (amniocentesis)
      - Cell-free DNA testing (newest method)

# Diagnosis of Severity of Anemia

- If you don’t have paternal status or fetal antigen status available
  - Serial maternal antibody titers until critical titer reached (>1:8)
- Once critical maternal antibody titer > 1:8
  - Confirm fetal antigen status (via amnio or cfDNA)
  - Begin Middle Cerebral Artery (MCA) doppler assessment via US

# Pathophysiology of Fetal Anemia



# Assessment of the Severity of Fetal Anemia

## Historical Perspective

- Once anemia suspected by maternal antibody screening and titers
  - Serial amniocentesis performed
  - Perform light absorption test (increased bilirubin in fluid leads to greater light absorption at 450 wavelength)
- Liley Curves developed to assess risk of fetal anemia (>28 weeks)
  - **Zone I**
    - Limited hemolysis
      - No risk of fetal death
  - **Zone II**
    - Hemolysis present
      - Intermediate risk of fetal death
      - Warrants frequent tests
  - **Zone III**
    - Extensive hemolysis
      - Increased risk of fetal death
- Limitations of Liley Curves
  - Required serial amniocentesis
  - Degree of hemolysis not assessed
  - Normative values only to 28 weeks

# Current Method of Assessment of Fetal Anemia

- Basic physiology
  - Hemolysis – decreased hematocrit
  - Lower hematocrit – less viscous blood
  - Less viscous fluid – flows faster
- Fetal brain stem is vital to survival
- Middle Cerebral Artery (MCA) bathes the brainstem
- During periods of stress or trauma (ie fetal anemia), autoregulation shunts blood to MCA leading to faster flow/increased $O_2$ delivery
- Peak systolic flow of MCA increases

# Measurement of the Peak Systolic Velocity of the Middle Cerebral Artery (PSV–MCA)

- Reliable method to determine degree and severity of fetal anemia
- PSV-MCA >1.5 multiples of median (MoMs)
  - Indicates fetal response to anemia by delivering more oxygenated blood to brainstem (autoregulation adaptation)

# Severity of Anemia

- When PSV-MCA > 1.5 MoMs
  - Indicates Hgb <5% or Hct <15%
- Warrants Percutaneous Umbilical Cord Blood Sampling (PUBS) of the fetus
- 2009 Meta analysis (25 studies/1639 participants) of the validity of doppler analysis to determine fetal anemia
  - Dx of fetal anemia confirmed
    - Sensitivity 75%
    - Specificity 90%
  - Use of serial MCA determinations decreases false positive rate <5%

# The PSV-MCA

- Initially developed to screen for fetal anemia due to red cell autoimmunization
- Since its initial use – now validated
  - Parvo B19 Infection (all viruses now included)
  - TTTS Surveillance
  - Fetal-Maternal Hemorrhage

# How often should MCA Dopplers be done?

- Once risk factors for fetal anemia are identified
  - Serial testing of critical antibody thresholds reached (typically >1:8 or positive IgM/IgG antibodies)
  - Frequency of testing should take into account
    - Prior Obstetric History
    - Gestational Age
    - Prior MCA Values/Trends

# When should MCA Dopplers start?

- As a rule –
  - Start MCA dopplers when a PUBS/Intrauterine Transfusion (IUT) can be technically performed (18-20 weeks)
  - At viability (~24 weeks) MCA dopplers should be weekly unless “trend” dictates more frequently.

# What are the parameters and management schemes after PUBS?

- Percutaneous Umbilical Cord Blood Sampling (PUBS) indicated when PSV-MCA >1.5 MoM
  - If fetal hematocrit >30% - no transfusion needed
  - If fetal Hct <30%, transfuse to a fetal Hct of 40-50%
    - Transfused blood:
      - O negative
      - Negative antibody screen
      - CMV negative
      - Irradiated
      - High Hct 75-85%

# Once an intrauterine transfusion is performed, what is the management plan?

- Depending on Gestational Age, a second IUT is needed (usually within 10-14 days)
- As a rule, the fetal Hct usually drops 1% day
- Anemia due to Parvo Infection typically responds to a single IUT
- Follow up PSV-MCA should be done serially (1-2x/wk)
  - New threshold for repeat IUT is 1.69 MoM
- Most MFMs don’t do IUT’s past 35 weeks

# Timing of Delivery

- No high-quality data to direct care
- Expert opinion says 36-38 weeks with reassuring fetal testing
- Balance
  - Risk of fetal stillbirth
  - Risk of another PUBS/IUT (PPROM/Infection/Demise)
  - Risk of morbidity of fetal/neonatal hyperbilirubinemia
- At time of delivery
  - Compatible fetal blood should be immediately available for transfusion post-delivery

# Short-term Neonatal Outcomes with the use of IUT

- Overall perinatal mortality in severe fetal anemia has decreased to less than 10%
- Post-natal management of hemolytic disease centers on
  - hyperbilirubinemia with phototherapy
  - exchange transfusions to prevent kernicterus.
- Database from Sweden (20 years experience)
  - 284 IUT's in 86 pregnancies in 72 women
  - 80 live births/mean GA – 36 weeks
    - 19 (24%) born prior to 34 weeks
    - Mean hospital stay 8 days
      - 97% phototherapy
      - 62% exchange transfusions

# Long-term Outcomes following IUT

## Maternal

- Increased risk of developing immunization to additional antigens
  - 25% developed additional antibodies after IUT
  - > 70% developed multiple red cell antibodies in postpartum period

# Long-term Outcomes following IUT

## Fetus/Neonate

- Overall survival rate close to 90%
- % survival varies with
  - Experience of operator
  - Delivering center
  - Presence of fetal hydrops

# Long-term Outcomes following IUT

**LOTUS** Study (**lo**ng **t**erm follow **u**p after intrauterine tran**s**fusions)

- Largest study on neurodevelopmental outcomes in children treated in utero with intrauterine transfusion (IUT)
  - 291 children (2-17yo) underwent IUT for red cell alloimmunization over 20 years (1988-2008)
    - Rh(D) – 80%
    - Kell – 12%
    - c – 5%
    - Other - 2%

# LOTUS OUTCOMES (cont.)

- Overall survival rate – 90%
- Incidence of neurodevelopmental impairment – 4.8%
  - (CP, severe developmental delay)
- These outcome rates for neurodevelopment impairment were increased in setting of fetal hydrops
- Setting of hydrops Odds Ratio (OR) – 4.3
    - Mild hydrops OR – 4.3
    - Severe hydrops OR – 9.9
    - Preterm birth <32 wks OR 12.8

# LOTUS OUTCOMES (cont.)

- Perinatal Survival rates for Parvo B19 following IUT are lower
  - Survival rates lower (67-85%)
  - Likely a consequence of later diagnosis of severe anemia with hydrops because of unknown maternal exposure