Current Diagnosis and Management of Red-Cell Alloimmunization

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At the end of this presentation, the participants will be able:

- To Describe
  - The Rh alloimmunization story
  - The role of Doppler ultrasound of the middle cerebral artery in fetal anemia
  - The standard of care for the diagnosis and management of fetal anemia
Definition of fetal anemia

Hemoglobin value below the 5th percentile (2 SD; 95% CI) for gestational age
Causes of fetal anemia

• Red blood cell alloimmunization
• Infections
• Fetomaternal hemorrhage
• Twin-twin-transfusion syndrome
• Thalassemia
• Enzymopathies
• Fanconi anemia
• Diamond-Blackfan anemia
Before 1968

>10,000 deaths in the USA for HDN
Rh hemolytic disease

United States

~ ??? cases per year

Rhogam (1968)
“Irregular” red blood cell antigens

<table>
<thead>
<tr>
<th>Blood group system</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh</td>
<td>C, c, e, E</td>
</tr>
<tr>
<td>Kell</td>
<td>K, k, Ko, Kpa, Kpb, Js, Js</td>
</tr>
<tr>
<td>Duffy</td>
<td>Fya, Fyb, Fy3</td>
</tr>
<tr>
<td>Kidd</td>
<td>Jka, Jkb, Jk3</td>
</tr>
<tr>
<td>MNSs</td>
<td>M, N, S, s, U, Mi, Mt, Vw, Mur, Hil, Hut</td>
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<tr>
<td>Lutheran</td>
<td>Lua, Lub</td>
</tr>
<tr>
<td>Diego</td>
<td>Dia, Dib</td>
</tr>
<tr>
<td>Xg</td>
<td>Xga</td>
</tr>
<tr>
<td>P</td>
<td>PP1p(Tja)</td>
</tr>
<tr>
<td>Public antigens</td>
<td>Yta, Ytb, Lan, En, Ge, Jra, Co, Co</td>
</tr>
<tr>
<td>Private antigens</td>
<td>Batty, Becker, Berrens, Biles, Evans, Gonzales, Good, Heibel, Hunt, Jobbins, Radin, Rm, Ven, Wright, Wright, Zd</td>
</tr>
</tbody>
</table>
Karl Landsteiner
Nobel prize in Physiology/Medicine (1930) for his discovery of human blood groups (1901)
Philip Levine, MD
RH and Fetal hemolytic disease (1937-1941)
Rh – Medical Discoveries

K. Landsteiner - A,B,O phenotypes: 1901

K. Landsteiner and Wiener - anti-Rh: 1940

P. Levine - anti Rh cause of HDN: 1941

D. Bevis - Amniocentesis in HDN: 1953
Albert William Liley
DeltaOD450 (1961)
Rh-Cell Alloimmunization: The Story
Vincent Freda and John O. Gorman (1968)
Rhogam
Cyril A. Clarke
Ronald Finn
Vincent J. Freda
John G. Gorman
William Pollack

Lasker award in 1980
Fetoscopy

A) Diagnosis of open spina bifida
B) Fetal blood sampling

Valenti C. Am J Obstet Gynecol 1973;11:581
Fernand Daffos
Cordocentesis (1983)
Cord blood sampling

Amniocentesis  Cordocentesis

Fetal Anemia
Blood velocity in anemia

↓ Viscosity  ↑ CO

↑ Velocity
Christian J. Doppler was an Austrian physicist who described the Doppler effect in 1842.

Doppler Formula

\[ F_d = \frac{2(F_c \times V \times \cos \alpha)}{C} \]
Angle Dependence

\[ 2(fc \cdot \cos A \cdot V) \]

\[ fd = \frac{c}{\text{c}} \]
Middle Cerebral Artery Peak Systolic Velocity
Where to sample the MCA?
It is easy to sample the MCA with an angle of zero degrees, which allows for the real velocity of the blood flow to be determined.

These are the steps for the correct sampling of the middle cerebral artery peak systolic velocity.

The use of an angle corrector increases the intra- and inter-observer variability; therefore, its use is not recommended.
Prospective study on an intention to treat

- Multicenter study in 5 tertiary referral centers
- 125 fetuses at risk for anemia
- MCA-PSV used for timing a cordocentesis

• MCA PSV single value: False positive rate: 12%

• MCA PSV trend: False positive rate: <5%

Doppler Ultrasonography versus Amniocentesis to Predict Fetal Anemia

Dick Oepkes, M.D., P. Gareth Seaward, M.B., B.Ch.,
Frank P.H.A. Vandenbussche, M.D., Rory Windrim, M.B., John Kingdom, M.D.,
Joseph Beyene, Ph.D., Humphrey H.H. Kanhai, M.D., Arne Ohlsson, M.D.,
and Greg Ryan, M.B., for the DIAMOND Study Group*
ACOG PRACTICE BULLETIN

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Management of Alloimmunization During Pregnancy
All Truth Passes Through Three Stages:

• First It Is Ridiculed
• Second It is Violently Opposed
• Third It is Accepted As Being Self-Evident

A. Schopenhauer
Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline #8: The fetus at risk for anemia—diagnosis and management

Society for Maternal-Fetal Medicine (SMFM); Giancarlo Mari, MD; Mary E. Norton, MD; Joanne Stone, MD; Vincenzo Berghella, MD; Anthony C. Sciscione, DO; Danielle Tate, MD; Mauro H. Schenone, MD
Management of Alloimmunization

**Rh D Alloimmunization**

- Fist Affected Pregnancy
  - 2-4 weeks interval titer surveillance
  - Critical titer
  - Paternal and/or fetal genotyping
    - Fetus at risk
      - MCA-PSV surveillance
        - >1.5 MoM
          - <35 weeks: FBS
            - Anemia: IUT
            - Not Anemic: Continue MCA-PSV surveillance
          - >35 weeks: MCA-PSV trending up
            - Delivery
          - MCA-PSV stable
            - IOL 39 weeks
          - <1.5 MoM: Continue surveillance
    - Fetus not at risk
      - Routine prenatal care
- Previously Affected Pregnancy
Intrauterine transfusion

Overall rate of complications of 3.3% per fetus and 1.2% per procedure

A fetal loss rate of 17% when the fetal blood sampling is performed at < 20 weeks.

Intrauterine transfusion

• **VOLUME TO TRASFUSE INTRAVASCULARLY**  = (Desired hematocrit-Fetal hematocrit/Donor hematocrit-desired hematocrit) x Fetoplacental volume

• **VOLUME TO TRANSFUSE INTRAPERITONEALLY**  = (GA in weeks – 20 ) x 10
Transfusion Intervals

- The MCA-PSV hold its negative predictive value and may be factored when planning subsequent IUT intervals.

- A recent randomized trial, that compared timing of subsequent transfusions with the use of the MCA-PSV (serial upward trend of values > 1.5 MoM) vs. expected decrease in fetal hematocrit found no differences in mean hemoglobin levels at birth, number of IUT procedures or in the rates of adverse infant outcomes.

PETIT study: retrospective study in 12 fetal therapy centers, of early onset, (<13 weeks of gestation) intrauterine immunoglobulin treatment, of pregnancies previously affected by severe hemolytic disease of the fetus and newborn (HDFN)

Results suggested that IG therapy may delay the onset of severe anemia and may decrease the incidence of hydrops and the need of newborn exchange transfusion

Is the MCA-PSV reliable for the diagnosis of fetal anemia due to other causes?
Which patients are candidates for the assessment of the MCA-PSV?

- Patients at risk for having an anemic fetus
- Indiscriminate use of the MCA-PSV may cause more harm than good
Conclusion

RH story

• A successful story in Fetal Medicine
• Mirror of what is happening in Fetal Medicine

First “Do no harm”
Case 1

History

- 33 yo, G3 P0 Rh sensitized (anti D = 1/64)
- Fetus is Rh positive
- Rising delta OD\textsubscript{450} in amniotic fluid
Delta OD_{450}

Gestational age (weeks)
Case 1

History

- 33 yo, G3 P0 Rh sensitized (anti D = 1/64)
- Rising delta $\text{OD}_{450}$ in amniotic fluid
- Fetus is Rh positive
- Cordocentesis at 22 weeks (unsuccessful)
- Referred at 22.1 weeks’ gestation
Anti D = 1/256

Middle Cerebral Artery Peak Systolic Velocity

- Hgb = 5.5 g/dL, MCA-PSV 70cm/S
- Hgb = 7.4 g/dL, 50cm/s
- Hgb = 9.0 g/dL

Median MoM

Anti D = 1/256

Gestational Age (wks)
Gestational Age (weeks)

18 20 22 24 26 28 30 32 34 36 38 40

Hemoglobin (gr/dl)

4 5 6 7 8 9 10 11 12 13 14 15 16 17

Severe Anemia
Moderate Anemia
Mild Anemia

95 50 5
Is the delta OD_{450} better than MCA-PSV or vice versa?

- Am J Obstet Gynecol 1997 (SMFM);180:18