The Rh Problem: Past and Future Concerns

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Rhesus Isoimmunization

- Rh-negative immunized mother
- Rh-negative unaffected baby
Rhesus Isoimmunization

- Rh-negative immunized mother
- Rh-positive hydropic stillborn baby
Ultimate Failure
Rh Erythroblastosis Fetalis

- Hydrops fetalis known to Hippocrates
- 1937 Weiner discovers Rh factor
- Prior to 1950s Rh affected newborns were managed by general practitioners in nursery
- 1950s many neonatal advances
- 1956 Allen and Diamond – exchange transfusion
1960s Decade of Fetal Medicine

CONCEPT OF HIGH-RISK SPECIAL CLINICS

1961  Liley - amniotic fluid OD450 graph
1962  Saling - fetal scalp blood sampling
1963  Liley - IUT for Rh-immunization
1965  Steele and Bregman - culture AF cells
1966  Parkman and Myer - rubella immunization
1969  Freda et al - postpartum RhIg prophlaxis
THE 1960s

- We shall look the 1960s, then subsequent advances for:
  - Diagnosis
  - Treatment
  - Rh Prophylaxis
1960s ARMAMENTARIUM

- Rh-antibody titers = fetal risk
- Amniograms = condition
- AF òOD450 = condition
- Fetal transfusions = treatment
- Preterm delivery
### Indirect Coombs: Titers

<table>
<thead>
<tr>
<th></th>
<th>1:32 or lower</th>
<th>1:64 or higher</th>
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<tbody>
<tr>
<td>IUD &lt; 37 weeks</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Alive at 37 weeks</td>
<td>187</td>
<td>154</td>
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</tbody>
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*Allen, Diamond, Jones. *NEJM.* 251: 453, 1954*
AF ΔOD450

Click icon to add chart

![Absorbance vs Wavelength Graph with peak at 480 nm]
Liley, *AJOG* 1963;86:485
SUBSEQUENT ADVANCES
AF ΔOD450 Zones

Queenan, AJOG
1993;168:1370
Physiologic Changes in Fetal Anemia

- $\frac{2}{8}$ Fetal cardiac output
- $\frac{235}{92}$ Blood viscosity due to $\frac{235}{92}$ hematocrit
- $\frac{2}{8}$ Blood velocities
Rh Immunization
Middle Cerebral Artery

74% Positive Predictive Value
10% False Positive

Mari et al, *NEJM* 2000; 342: 9

55% Positive Predictive Value
98% Negative Predictive Value

Zimmerman et al, *BJOG* 2002;109:342
MCA Doppler

- AF à OD450 and MCA Doppler compared using fetal hgb
- MCA Doppler as accurate or better than AF à OD450
- Noninvasive

Oepkes AJOG; 191; 2004 (Leiden)
MS Fetal RhD Genotype by cff DNA

- 283/285 fetal RhD genotypes
- 2 cases of maternal Rh gene not expressed in phenotype
- No false positives
- No false negatives

Gautier E et al. *AJOG* 2005: 192;666-9
FETAL THERAPY
SUBSEQUENT ADVANCES
Intravascular IUT

- Seven different approaches
- All fetuses (411) - good outcomes: 84%
- Nonhydropic - good outcomes: 94%
- Hydropic - good outcomes: 74%
- Those with anemia but no hydrops at IUT were 5X more likely to survive
- Safe procedure, 1-3% perinatal loss rate

Schumacher and Moise Obstet Gyn 1996; 88: 137
IUT Hydrops Fetalis

- 210 fetuses
- 208 pregnancies
- 593 transfusions
- Survival overall: 86%
- Survival hydrops: 78%
- Procedure loss: 1.7%

Van Kamp et al. *Acta O/G Scan* 2004: 83;731 (Leiden)
Long Term Follow-up after intrauterine transfusions: The LOTUS Study

- Long term neurodevelopmental outcome in children treated with intrauterine transfusion 1988-2008 Leiden University Medical Center
- Neurodevelopmental impairment: at least one
  - Cerebral palsy
  - Severe developmental delay
  - Bilateral deafness and/or blindness

  » Lindenberg, Oepkes, Van Kamp et al
  Leiden, BMC 2010 Dec 1
Long Term Follow-up after intrauterine transfusions: The LOTUS Study

RESULTS

- Perinatal survival 91% (389/426)
- Complete data in 87% (338)
- NDI detected in 9% (31/338)
  - Bilateral deafness (3)
  - Cerebral palsy (5)
  - Severe developmental delay (23)
Univariate analysis showed factors associated with NDIs:

- Hemoglobin at first IUT ($p=0.032$)
- Presence fetal hydrops ($p=0.001$)
- Number of IUTs ($p=0.016$)
- Severe neonatal morbidity ($p=0.003$)
Fetal Therapy

Intraperitoneal IUT – rarely used

Operative fetal transfusion - radical

Fetoscopy - obsolete

Intravascular IUT – standard technique
  umbilical vein
  intrahepatic IVC
2016 Armentarium

- MS fetal Rh status = fetal risk
- Rh-antibody titers = fetal risk
- Sonography = age and condition
- MCA PSP = fetal condition
- Fetal transfusions = treatment
- Preterm delivery = prevent IUD
Rh-Immune Prophylaxis
Postpartum Immununization

- Fetal and maternal circulations were separate
Factors which contribute to passage of fetal RBCs into the maternal circulation:

- Trendelenberg Position
- Anesthesia
- No ecbolic

ABO Protection

- When the fetus is incompatible with the mother in the ABO system, it confers protection against Rh-immunization.
- Fetal RBCs are destroyed in the maternal circulatory system.
Mechanism of Rh – Immune Prophylaxis

Active Immunization

Antigen → Antibody Response

Passive Immunization

Antigen + Antibody Excess → No Antibody Response
Passive Immunization Protection

- Since most (90%) of immunizations occurred postpartum, perhaps passive immunization could provide protection against active immunization.
Sept 9, 1965 Singer calls secret meeting Waldorf Astoria to discuss the results of the trials which were added sequentially posted on a blackboard.

Following meeting Ortho participants would not comment.

The clinical investigators emerged elated and could see no reason to keep secrets: John Gorman, Vince Freda, Alvin Zipursky, and I seated in a bar discussing the six month results: 0/92 treated versus 21/94 controls.

Do these figures have statistical significance? Asked Zimmerman.

“As the figures were posted on the blackboard we could see it was proven” added John Gorman.

David Zimmerman *Rh: The intimate history of a disease and its conquest*

Rh-Immunoglobulin

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<td>NO RhIG</td>
<td>13%</td>
</tr>
<tr>
<td>PP RhIG</td>
<td>1.3%</td>
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SUBSEQUENT ADVANCES
<table>
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<tr>
<th>Rh – negative status</th>
<th>Count (%)</th>
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<tr>
<td>Primigravida</td>
<td>45 (1.6%)</td>
</tr>
<tr>
<td>ABO Compatible</td>
<td>44 (1.9%)</td>
</tr>
<tr>
<td>ABO Incompatible</td>
<td>1 (0.2%)</td>
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Bowman, et al
Rh Immunoprophylaxis
## Rh-Immunoglobulin

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<tr>
<td>AP + PP RhIG</td>
<td>0.16%</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Y</td>
<td>391</td>
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\[ X = \text{PP Rh Immune Prophylaxis} \]
\[ Y = \text{28 weeks Rh Immune Prophylaxis} \]
FUTURE CONCERNS

- Fewer and less severe cases
- Passive immunity is not a cure
- “Weak D” genetically defined
- Avoidance of AP RhIG with Rh-negative fetus
- Fewer IUT centers
- More irregular antibodies
- Genetically engineered RhIG
Fewer Rh immunized pregnancies

- RhIG has been effective and consequently the number of RhD - alloimmunized pregnancies is markedly decreased
- Decreased size of families decreases the severity
- Severe cases of RhD erythroblasosis fetalis will still occur
Passive Immunity is not a cure

- RhIG has been very successful in decreasing disease
- Unlike most immunization programs (rubella, polio etc) the protection is temporary
- RhIG provides passive to prevent active immunization
- RhIG must be given for each antigen exposure
- Incompatible transfusion: RhIG 300 micrograms covers 30ml Rh-positive blood
- Sufficient RhIG given when indirect Coombs test turns positive
- Tubal litigation at cesarean – give RhIG
Weak D Clinical Management

• Weak D (formerly Du positive) can now be managed better
• By genotyping, those with weak D, types D1, 2, or 3 may be treated as RhD – positive
• The genotype does not need repeating
• This can result in major changes in management
Figure 1

3,953,000 Live births

3,812,000 Pregnancies

556,500 RhD-negative

16,700 Serologic Weak D

13,360 weak D types 1, 2 or 3

24,700 unnecessary ante- and postpartum Rhlg injections

RHD Genotyping
Figure 2

5,000,000 Individuals Transfused Annually in US

730,000 RhD Negative

21,900 Serologic Weak D

17,520 weak D types 1, 2 or 3

Could receive RhD+ Units (47,700 units)

RHD Genotyping
Avoiding unnecessary AP RhIG

- Several European countries are testing MS RhD status of the fetus
- These programs eliminate the administration of RhIG in mothers with RhD-negative fetuses

Clausen FB et al. Report of the first nationally implemented clinical screening for fetal RhD to ascertain the requirement for antenatal RhD prophylaxis. *Transfusion* 2012; 52: 752-8
Avoiding unnecessary AP RhIG

- Such programs are under consideration in the USA
- The technology is now available *
- Cost effectiveness studies are process

* Moise KJ Jr et al. *Circulating Cell-free DNA to Determine Fetal RHD Status in all three Trimesters of Pregnancy*. Vol 128 no.6 December 2016 OBS&GYN
Fewer Centers for IUTs

- Based on a survey of all of the medical centers with MFM fellowships, there are fewer sites with experience in fetal transfusions.
- Patients with need for fetal transfusions should be referred to centers with sufficient experience.
- These capabilities will vary over time.
Rh-Immunophrophylaxis: Current

- Pooled human plasma from actively immunized men
- Cost of production
- Infection – Hepatitis C ‘91-94 (not in USA)
- Risk to volunteers
- Supply - limited
Rh-Immunoprophylaxis: Future

- Registered with Clinical Trials. Gov: dose finding study LFB953 using monoclonal antibody RhIG
- Planned clinical trials in Germany and USA
- Polyclonal antibody RhIG
- Advantages:
  - cost
  - purity
  - availability
REFERENCES


• ACOG. Prevention of Rh D alloimmunization. ACOG Practice Bulletin No. 4 Washington DC ACOG, 1999