Fetal middle cerebral artery Doppler to time second and subsequent intrauterine transfusions to treat anaemia due to red cell alloimmunisation: A randomised trial

Professor Jodie M Dodd
Declaration of Interests

• None
An international collaboration...

- J Dodd
- C Andersen
- J Dickinson
- J Louise
- A Deussen
- R Grivell
- L Voto
- M Kilby
- R Windrim
- G Ryan
- G Voto
- G Saa
- G Gardener
- J Thomas
- P Muller
- C Wilkinson
- C Crowther
- P Devlieger
- J Richter
- G Sander
- F Audibert
- G Seaward
- A Skoll
- P McParland
- R Moore
- C Sreenan
- E Parry
- J Tuohy
- S Pretlove
- A Cameron
- P Wu
- S Court
Diagnosis of Fetal Anemia: MCA Doppler Assessment


Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization

G. Marti*, A. Adrignolo*, A. Z. Abuhamad†, J. Pirhonen*, D. C. Jones*, A. Ludomirsky** and J. A. Copel*

*Departments of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut; †Baylor College of Medicine, Houston, Texas; ‡Eastern Virginia Medical School, Norfolk, Virginia; and **Pennsylvania Hospital, Philadelphia, Pennsylvania, USA

The middle cerebral artery blood velocity increases with advancing gestation and is a non-invasive method of detecting anemia in pregnancies complicated by maternal blood group immunization.
Diagnosis of Fetal Anemia: MCA Doppler Assessment

- Fetal anaemia
  - Blood viscosity
  - Cardiac Output
    - Hyperdynamic fetal circulation
    - Assessment of fetal MCA PSV
Aim

- For a fetus with red cell alloimmunisation who has undergone one IUT
  - can Doppler MCA-PSV be used to time second and subsequent transfusions
  - compared with estimating the fall in fetal haematocrit or haemoglobin
  - without compromising neonatal haemoglobin at birth
Trial Entry

• Inclusion
  – Singleton pregnancy
  – Fetal anaemia secondary to red cell alloimmunisation
  – Fetus has undergone a previous IUT

• Exclusion
  – Fetal anaemia secondary to any other cause
  – Known fetal chromosomal anomaly

• Randomisation
  – On-line system, computer generated schedule
  – Stratification for
    • presence or absence of hydrops at first IUT
    • Type of antibody (Kell versus other)
Timing second & subsequent transfusions:
Predicting the rate of red cell destruction

• Estimated Fall in Fetal Haematocrit
  – 1% per day
    • Moise 1989 Fetal Diag Ther

• Estimated Fall in Fetal Haemoglobin
  – 0.3g/dL per day
    • Scheier 2006 AJOG
Timing second & subsequent transfusions: MCA-PSV

Post transfusion chart

- A: moderate to severe anaemia
- B: mild anaemia
- C: no anaemia

MCA peak velocity (cm/sec)

Gestational age (weeks)

1.69 MoM

1.32 MoM

Median

Copyright of speaker
Outcomes

• Primary
  – Infant Haemoglobin (measured at birth)

• Secondary
  – Adverse infant outcomes related to alloimmunisation
    • Stillbirth or neonatal death; severe fetal anaemia; severe neonatal anaemia; need for neonatal exchange transfusion
  – Procedure related complications necessitating delivery
    • PPROM; PTL; chorioamnionitis; placental abruption
  – Infant complications
    • Preterm birth before 34 weeks; jaundice; NICU admission; top-up transfusion
Sample Size & Analyses

- 35 participants per group; 70 in total
- 80% power (2-sided alpha 0.05) to detect non-inferiority with a margin of 0.6g/dL in haemoglobin at birth
- Intention to treat analysis
- No imputation for missing data
- Both unadjusted and adjusted analyses
  - Adjustment for stratification variables
Flow of Participants

75 Women Consented & Randomised

MCA-PSV Group
N=37

- Excluded
  N=1

- Included in Analyses
  N=36

  3 Neonatal Deaths

Fall Fetal Hct Group
N=38

- Excluded
  N=3

- Included in Analyses
  N=35

  1 Stillbirth;
  2 Neonatal Deaths

Included in Analyses
N=35
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCA-PSV Group</th>
<th>Estimated Fall in Fetal Hct Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=36</strong></td>
<td>33.97 (4.78)</td>
<td>33.12 (4.67)</td>
</tr>
<tr>
<td>Maternal Age: Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Antibody: N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Kell</td>
<td>2 (5.56)</td>
<td>5 (14.29)</td>
</tr>
<tr>
<td>- Other</td>
<td>34 (94.44)</td>
<td>30 (85.71)</td>
</tr>
<tr>
<td>Hydrops at First Transfusion: N (%)</td>
<td>5 (13.89)</td>
<td>5 (14.29)</td>
</tr>
<tr>
<td>Gestational Age (wks) at Randomisation:</td>
<td>30.29 (27.71, 32.07)</td>
<td>30.29 (27.71, 31.86)</td>
</tr>
<tr>
<td>Smoker: N (%)</td>
<td>5 (13.89)</td>
<td>5 (14.29)</td>
</tr>
<tr>
<td>Weight at Trial Entry (kg): Mean (SD)</td>
<td>70.32 (18.02)</td>
<td>71.63 (12.39)</td>
</tr>
<tr>
<td>Height at Trial Entry (kg): Mean (SD)</td>
<td>163.39 (5.89)</td>
<td>161.00 (6.76)</td>
</tr>
<tr>
<td>Ethnicity: N(%)</td>
<td></td>
<td></td>
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<tr>
<td>- Caucasian</td>
<td>22 (61.11)</td>
<td>21 (60.00)</td>
</tr>
<tr>
<td>- Hispanic</td>
<td>9 (25.00)</td>
<td>9 (25.71)</td>
</tr>
<tr>
<td>- Asian</td>
<td>2 (5.56)</td>
<td>2 (5.71)</td>
</tr>
<tr>
<td>- Other</td>
<td>3 (8.33)</td>
<td>3 (8.57)</td>
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## Fetal & Neonatal Outcomes

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<thead>
<tr>
<th>Outcome</th>
<th>MCA-PSV Group (N=36)</th>
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<tr>
<td>Mean cord haemoglobin (g/dL)</td>
<td>103.62 (38.20)</td>
<td>120.26 (31.40)</td>
<td>-15.58 (-32.43, 1.26)</td>
<td>0.090</td>
</tr>
<tr>
<td>Number of IUTs performed</td>
<td>1.75 (1.79)</td>
<td>1.80 (1.32)</td>
<td>0.88 (0.61, 1.26)</td>
<td>0.474</td>
</tr>
<tr>
<td>Adverse fetal or neonatal outcome*</td>
<td>28 (82.35)</td>
<td>26 (77.57)</td>
<td>1.06 (0.82, 1.37)</td>
<td>0.660</td>
</tr>
<tr>
<td>Severe fetal anaemia*</td>
<td>23 (65.71)</td>
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<td>0.90 (0.65, 1.25)</td>
<td>0.539</td>
</tr>
<tr>
<td>Mean Gestational Age at Birth</td>
<td>35.23 (2.30)</td>
<td>35.07 (2.28)</td>
<td>0.26 (-0.75, 1.27)</td>
<td>0.613</td>
</tr>
<tr>
<td>Mean Birthweight</td>
<td>2581.11 (644.03)</td>
<td>2602.69 (591.34)</td>
<td>-49.79 (-246.14, 146.57)</td>
<td>0.619</td>
</tr>
<tr>
<td>NICU Admission</td>
<td>28 (80.00)</td>
<td>23 (67.75)</td>
<td>1.20 (0.89, 1.60)</td>
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<tr>
<td>Severe anaemia at birth*</td>
<td>11 (34.38)</td>
<td>7 (22.58)</td>
<td>1.40 (0.63, 3.13)</td>
<td>0.406</td>
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<tr>
<td>Neonatal Exchange Transfusion*</td>
<td>14 (40.00)</td>
<td>9 (26.47)</td>
<td>1.42 (0.71, 2.83)</td>
<td>0.316</td>
</tr>
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<td>Neonatal Top-up Transfusion</td>
<td>21 (60.00)</td>
<td>19 (55.88)</td>
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### Maternal & Procedure Related Outcomes

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<thead>
<tr>
<th>Outcome</th>
<th>MCA-PSV Group (N=36)</th>
<th>Estimated Fall in Fetal Hct / Hb Group (N=35)</th>
<th>Unadjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened preterm labor</td>
<td>2 (5.56)</td>
<td>3 (8.57)</td>
<td>0.623</td>
</tr>
<tr>
<td>PPROM</td>
<td>1 (2.78)</td>
<td>0 (0.00)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Placental Abruption</td>
<td>0 (0.00)</td>
<td>1 (2.86)</td>
<td>0.493</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>0 (0.00)</td>
<td>1 (2.86)</td>
<td>0.493</td>
</tr>
<tr>
<td>Preterm birth before 34 weeks</td>
<td>9 (25.00)</td>
<td>7 (20.00)</td>
<td>0.616</td>
</tr>
</tbody>
</table>
Comparisons with other studies

• Procedure related risk of complications: 2.8%
• Overall survival rate: 93%
  – Consistent with 3.1%, & >90% reported (van Kamp 2005)
  – Higher than the 1.2% & 97% reported 2001-2014 (Zwiers 2016)

• Differences
  – Likely reflect pragmatic multicentre study vs single tertiary referral centre with high case volume and clinician expertise
Limitations

- Modification of sample size from original trial registration
  - To reflect recruitment rates and allocated funding
  - Well powered to detect differences in Hb at birth
  - Underpowered to detect differences in other clinical outcomes

- Slower than anticipated recruitment
  - Delays in obtaining ethical approval
    - Mean 10 months sites where recruitment subsequently occurred
    - Mean 18 months sites where recruitment did not occur
  - Collaborator time pressures & lack of research support
  - Delay between investigators providing in principal support & funding
    - Development of protocol October 2006
    - Funding available January 2010
  - Change in clinical equipoise
Conclusions

• Both Doppler MCA-PSV measurement and estimating the fall in fetal haematocrit can be used to time second and subsequent IUTs

• Considerations with Doppler MCA-PSV:
  – Lower mean Hb at birth
  – Increased need for neonatal exchange transfusion
  – Increased frequency antenatal appointments for ultrasound surveillance
Acknowledgements

• We are indebted to the women and their infants who participated in this trial

• NHMRC
  – Neil Hamilton Fairley Overseas Fellowship 2006-2009
  – Practitioner Fellowship 2010-2014; 2015-2019
  – Project grant funding 2010-2012

• Discipline Obstetrics & Gynaecology, & Robinson Research Institute, The University of Adelaide

• Women’s and Children’s Hospital, North Adelaide

• Fetal Medicine Unit, Mt Sinai Hospital and University of Toronto
Perinatal Deaths

• MCA-PSV Group: 3 neonatal deaths
  – Hydropic fetus; death at 29 weeks following emergency preterm birth
  – Hydropic fetus; death at 30 weeks following emergency preterm birth
  – Death at 33 weeks secondary to liver failure following multiple exchange transfusions

• Estimated Fall in Fetal Hct Group: 1 stillbirth; 2 neonatal deaths
  – Stillbirth; hydropic fetus at 31 weeks; death occurred between randomization and scheduled second IUT
  – Preterm birth; no evidence of hydrops but severe anemia; complications of prematurity compounded by complex CHD
  – Preterm birth; no evidence of hydrops but severe anemia; complications of prematurity compounded by sepsis & multi-organ failure
# Previous pregnancies affected by alloimmunization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCA-PSV Group N=36</th>
<th>Estimated Fall in Fetal Hct Group N=35</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Pregnancies &gt;20wks: Median (IQR)</td>
<td>3.00 (2.00, 3.50)</td>
<td>1.00 (1.00, 4.00)</td>
<td>2.00 (1.00, 4.00)</td>
</tr>
<tr>
<td>1 Previous Pregnancy affected by Red Cell Alloimmunization: N (%)</td>
<td>14 (40.00)</td>
<td>12 (37.50)</td>
<td>26 (38.81)</td>
</tr>
<tr>
<td>2+ Previous Pregnancies affected by Red Cell Alloimmunization: N (%)</td>
<td>12 (34.29)</td>
<td>5 (15.63)</td>
<td>17 (25.37)</td>
</tr>
<tr>
<td>Of Pregnancies affected by Red Cell Alloimmunization: N (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Resulting in preterm birth</td>
<td>4 (15.38)</td>
<td>4 (23.53)</td>
<td>8 (18.60)</td>
</tr>
<tr>
<td>- Resulting in neonatal death</td>
<td>5 (19.23)</td>
<td>0 (0.00)</td>
<td>5 (15.15)</td>
</tr>
</tbody>
</table>
Original Sample Size Estimate

• A total of 536 women

• To detect a 30% reduction in a primary composite adverse outcome (De Boer 2008; Abdel Fattah 2005)
  – Stillbirth
  – Neonatal Death
  – Severe fetal anemia
  – Severe anemia at birth
  – Neonatal exchange transfusion

• 5% significance level; 90% power
Severe Fetal Anemia

• At the second or any subsequent transfusion

• Pre-transfusion haemoglobin ≥ 5 standard deviations below the mean for gestational age

• Mean Hb for gestational age defined according to the formula (Nikolaides Lancet 1988)
  – $Mean \ Hb = 11 + GA \text{ weeks} - 17 \times 0.19$
  – Standard Deviation 1g/dL
Care of women in both groups

• Surveillance prior to procedure

• Corticosteroids if GA >24 weeks

• Ultrasound guided technique by appropriately trained staff
  – Transfusion site
    • Clinician judgement
  – Fetal paralysis
    • Clinician judgement & local hospital practices
  – Transfused blood volume
    • GA, EFW, pre-transfusion haemoglobin

• Timing of birth
  – Clinician judgement & local hospital practices
Principal Findings

- Both Doppler MCA-PSV measurement and estimating the fall in fetal haematocrit can be used to time second and subsequent IUTs
  - Trend to lower haemoglobin at birth in MCA-PSV Group
  - Mean difference in Hb at birth: 103.6 vs 120.3
    - P=0.09
  - Trend to more neonatal exchange transfusions in MCA-PSV Group
    - 40.0% vs 26.5%
    - P=0.316

- No significant differences in other alloimmunisation or procedure related complications
  - Small event numbers
  - Underpowered