Background

- Brains MRIs of CHD patients are abnormal prior to surgery.

- Fetal cerebral blood flow is altered in CHD.
  - Donofrio 2003, Kaltman 2005

- Centralization, or redistribution of arterial blood flow to vital organs such as the brain, correlates with poor outcome in IUGR.

- Birth weight, HC, and growth in the first year of life are associated with developmental outcome.

Objectives

- To discuss early markers of neurodevelopment
- Fetal
  - Cerebrovascular resistance
    - CPR (cerebral-to-placental resistance ratio)
    - MCA PI (middle cerebral artery pulsatility index)
  - Biometry
    - Heart rate and HR variability
- Neonate
  - High density (128-lead) EEG measures of power and coherence
Methods

• Prospective, observational cohort study of CHD fetuses
  • hypoplastic left heart syndrome (HLHS)
  • d-transposition of the great arteries (TGA)
  • tetralogy of Fallot (TOF)
  • < 26 weeks gestational age (GA)

• Serial measures collected at:
  • 18-26 weeks GA (F1)
  • 27-33 weeks GA (F2)
  • 34-40 weeks GA (F3)

Fetal Doppler: MCA PI, UA PI, CPR
Fetal Biometry: HC, BPD, FL, AG, EFW
Fetal HR Variability: FHR, SD, IQR, RMSSD
Pre-op Neonatal EEG: power and coherence

BAYLEY SCALES OF INFANT DEVELOPMENT-III at 18-months of age
  • Cognitive, Language, Motor (100±15)

Middle Cerebral Artery PI z-score

PI = (PSV-EDV)/TAMX

Low PI estimates low resistance

Monica Maternal Abdominal fetal ECG
High Density 128-lead EEG

Methods: Statistics

• Associations between markers and ND tested
  • Pearson’s correlation coefficient significant at ≤0.05
    informed regression modeling by category
  • Univariate regression informed multivariable models for
    Cognition, Language, and Motor scores

Results

• 68 fetuses enrolled
  • 24 HLHS, 21 TGA, 23 TOF
  • 2 excluded due to genetic abnormalities
  • Neonatal EEG performed in 46 subjects at mean age 2.2±1.4 days
  • BSID-III performed in 46 (70%) at mean age of 18.6±0.6 months

<table>
<thead>
<tr>
<th>ND Score (normal: 100±15)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Score</td>
<td>95±11</td>
</tr>
<tr>
<td>Language Score</td>
<td>88±15</td>
</tr>
<tr>
<td>Motor Score</td>
<td>91±13</td>
</tr>
</tbody>
</table>

Bayley Scores by CHD Diagnosis

- Type
- TGA
- Hs-ASD
- ALL

- Motor
- Language
- Cognition

BSID Score

0 30 60 90 120
### Univariate Regression - DOPPLER

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Cognition Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Doppler</td>
<td>UA PI z-score at 27-33 weeks GA (B=5.3, P=0.001, R²=0.21)</td>
<td>UA PI z-score at 18-26 weeks GA (B=8.9, P=0.003, R²=0.27)</td>
<td>UA PI z-score at 18-26 weeks GA (B=8.1, P=0.001, R²=0.23)</td>
</tr>
<tr>
<td>CFR &lt; 1 ever (B=7.3, P=0.04, R²=0.11)</td>
<td>CFR &lt; 1 ever (B=14.5, P=0.011, R²=0.32)</td>
<td>CFR &lt; 1 ever (B=9.2, P=0.02, R²=0.17)</td>
<td></td>
</tr>
</tbody>
</table>

### Univariate Regression - BIOMETRY

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Cognition Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Biometry</td>
<td>PC/AC at 18-26 weeks GA (B=1.3, P=0.01, R²=0.16)</td>
<td>FL/RPD at 27-33 weeks GA (B=1.2, P=0.003, R²=0.11)</td>
<td>None</td>
</tr>
</tbody>
</table>

### Univariate Regression – Fetal HR

<table>
<thead>
<tr>
<th>SD (sec) at 34-40 wks</th>
<th>Cognition Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>B=1102, P=0.018, R²=0.21</td>
<td>B=1418, P=0.004, R²=0.29</td>
<td>B=1259, P=0.017, R²=0.22</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IQR (sec) at 34-40 wks</th>
<th>Cognition Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>B=789, P=0.002, R²=0.32</td>
<td>B=645, P=0.017, R²=0.21</td>
<td>B=663, P=0.008, R²=0.27</td>
<td></td>
</tr>
</tbody>
</table>

### Univariate Regression - EEG

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Cognition Score</th>
<th>Language Score</th>
<th>Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal EEG</td>
<td>Gamma band left parietal to right parietal coherence during active sleep (B=35.3, P=0.02, R²=0.35)</td>
<td>Delta band left occipital log power during active sleep (B=15.6, P=0.003, R²=0.22)</td>
<td>Theta band left frontal to right frontal coherence during quiet sleep (B=197, P=0.01, R²=0.56)</td>
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</tbody>
</table>
### Multivariable Regression Models

<table>
<thead>
<tr>
<th></th>
<th>Predictors</th>
<th>B</th>
<th>P-value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td>Mean HCAC</td>
<td>B=-352</td>
<td>P&lt;0.001</td>
<td>R²=0.74</td>
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<tr>
<td><strong>Language</strong></td>
<td>CPR&lt;1 Ever</td>
<td>B=16</td>
<td>P=0.003</td>
<td>R²=0.41</td>
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<tr>
<td><strong>Motor</strong></td>
<td>UA Pi z-score</td>
<td>B=21</td>
<td>P=0.01</td>
<td>R²=0.86</td>
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<tr>
<td></td>
<td>Theta Band Left Frontal to Right Frontal Coherence During Quiet Sleep</td>
<td>B=183</td>
<td>P=0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IQR 34-40 weeks Monica</td>
<td>B=324</td>
<td>P=0.03</td>
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</tr>
</tbody>
</table>

### Summary

- Lower umbilical relative to middle cerebral artery resistance was associated with higher Cognitive score.
- Larger fetal abdomen relative to head was associated with higher Cognitive score.
- Lower umbilical artery pulsatility was associated with higher Language score.
- Increased EEG coherence in the frontal regions was associated with higher Motor scores.
- Increased fetal HR variability was associated with higher Motor Scores.

### Conclusions

- Possible markers of risk include:
  - Higher placental resistance relative to cerebral resistance
  - Decreased fetal somatic growth
  - Diminished fetal heart rate variability
  - Diminished frontal connectivity

- These hypothesis-generating findings should support additional investigation into the impact of fetal growth on early childhood development.

### References