Antenatal Associations with BPD

Poznan, Poland - 2016

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Cincinnati Children’s Hospital
University of Cincinnati
Cincinnati, Ohio
# Financial Relationships

<table>
<thead>
<tr>
<th>Grant</th>
<th>GSK B&amp;M Gates Foundation</th>
<th>New strategies for antenatal steroid treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consulting</td>
<td>Chiesi Pharma</td>
<td>Treatment for BPD</td>
</tr>
<tr>
<td></td>
<td>B &amp; M Gates Foundation</td>
<td>Infant Mortality</td>
</tr>
<tr>
<td>Supplies</td>
<td>Fisher &amp; Paykel, NZ</td>
<td>Respiratory supplies for sheep studies</td>
</tr>
<tr>
<td></td>
<td>Chiesi Pharma</td>
<td>Surfactant for sheep studies</td>
</tr>
</tbody>
</table>

**RESOLUTION OF POTENTIAL CONFLICTS OF INTEREST:**
- All material is independent of industry produced content.
- Only material supported by published data and evidence-based guidelines will be presented.

*Note: ANS therapy is *not* approved by the FDA*
Antenatal Associations with BPD:

• Very premature delivery
• Fetal exposure to inflammation
• Lung maturation, RDS, ANS
• Fetal growth restriction
Major Pathways Contributing to BPD

Fetal Lung Development/Injury
- Prematurity
- Inflammation
- SGA
- Induced maturation, ANS

Fetal Events

Resuscitation

Injury

Ventilation

Inflammation

Oxygen

Repair

“Normal”

BPD

Months

Minutes

Months

Years

Ongoing Injury

Outcome
RDS, Treatments, and BPD in NICHD - NN Network
for Infants Born at 22-28 wks GA
2003 to 2007 (N=9575)

Stoll, et al., Pediatr, 2010
Severity of BPD vs Gestational Age - NICHD-NNN Data for 9575 Infants - 2003-2007
68% of Population had BPD

Stoll, et al., Pediatr, 2010
Bronchopulmonary Dysplasia in NICHD-NRN for infants 22-28 wks GA

Birth Year

Stoll, JAMA, 2015
The primary association with BPD is very preterm delivery.
Inflammation/Chorioamnionitis and Prematurity

- Spontaneous Preterm Labor: 45%
- Delivery because of maternal or fetal indications: 30%
- Premature preterm rupture of the membranes (PPROM): 25%
- Preterm labor

Goldenberg, et al., The Lancet, 2008
The biome of the uterine-fetal compartment during normal pregnancy has been minimally studied.

- Vaginal biome changes during pregnancy (Aagaard, et al., 2012)
- Placental biome is similar to mouth organisms (Aagaard, et al. 2014)
- There probably is an intra-amniotic biome
- The effects of the biome on fetal development are unknown.
Endometrial Microbial Colonization and Plasma Cell Endometritis

<table>
<thead>
<tr>
<th>% of Population 3 Months Post-Partum</th>
<th>Normal Term</th>
<th>Spontaneous Preterm</th>
<th>Indicated Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>303</td>
<td>375</td>
<td>142</td>
</tr>
<tr>
<td>GA prior Delivery (wks)</td>
<td>39.6</td>
<td>26.4</td>
<td>27.2</td>
</tr>
<tr>
<td>+ Endometrial cultures</td>
<td>81%</td>
<td>85%</td>
<td>79%</td>
</tr>
<tr>
<td>+ Plasma Cell Endometritis</td>
<td>33%</td>
<td>43%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Ureaplasma on Surface of Human Sperm

Christina Knox, Queensland Univ. of Technology
Ureaplasma is the Most Frequent Organism Associated with Preterm Delivery

PCR detection of Ureaplasma or Mycoplasma in 179 amniotic fluids collected at 15-19 weeks from asymptomatic women.

<table>
<thead>
<tr>
<th></th>
<th>PCR Positive</th>
<th>PCR Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureaplasma</td>
<td>13%</td>
<td>87%</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>6%</td>
<td>94%</td>
</tr>
<tr>
<td>PPROM</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>5 of 33</td>
<td></td>
</tr>
</tbody>
</table>

Perni, et al., AJOB/Gyn, 2004
• Preterm fetuses are frequently exposed to organisms

• Organisms may be present in “non-inflammatory” preterm deliveries – Preeclampsia

• Organisms may be culturable or identified only by PCR or sequencing

An Hypothesis: Effective innate host defense mechanisms must be present in endometrium, membranes, and amniotic fluid to protect the pregnancy.
Inflammation and Lung Development

Correlation of Chorioamnionitis with RDS and BPD in Ventilated Preterm Infants

<table>
<thead>
<tr>
<th></th>
<th>Chorioamnionitis</th>
<th>No Chorioamnionitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RDS</strong></td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>% BPD</strong></td>
<td>63%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Fetal Lung Responses to 4 mg Endotoxin given by Intra-amniotic Injection

Inflammatory Cells in BALF

Lung Cytokine mRNA

Apoptosis

Proliferation

Kramer, et al., AJRCCM, 283:L452, 2002
Effect of Interval from 20 mg IA Endotoxin to Delivery

Lung Volume - 40 cmH$_2$O (ml/kg)

Interval to Preterm Delivery

Sat PC - Alveolar Wash ($\mu$mol/kg)

Jobe, et al., AJRCCM, 2000
Lung Inflammation Caused by Intra-amniotic IL-1β in Preterm Rhesus Macaque Fetuses

Kallapur, J. Immunol, 2013
Effect of IA Endotoxin Given 7 Days Before Preterm Delivery on Lung Structure

Control

Endotoxin
Intra-amniotic Inflammatory Mediators Cause

- Chorioamnionitis
- Lung inflammation/injury
- Lung maturation
- Arrest of airspace septation
  - Phenotype of BPD
- Immune Modulation
Lung Cytokine Responses to Intra-amniotic LPS in Preterm Sheep

Time after Intra-amniotic LPS Exposures

Intra-amniotic LPS Induces “Cross-Responsiveness” and “Cross-Tolerance”

Kramer, et al., Innate Immunity, 2009
Antenatal exposure to infection/inflammation can cause in animal models:

- Very preterm delivery
- Lung maturation
- Immune modulation

What are clinical associations for BPD?
Meta-Analysis of Studies Correlating Chorioamnionitis with BPD

All Studies - 59
Histologic Chorio - 37 Studies
Clinical Chorio - 12 Studies
Combination - 5 Studies
Microbiologic - 5 Studies

Hartling, et al., 2011
## Confounders for Populations With and Without Chorioamnionitis for Occurrence of BPD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study #</th>
<th>Patient #</th>
<th>Weighted Mean Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>+ Chorio</strong></td>
</tr>
<tr>
<td>Gestational Age</td>
<td>24</td>
<td>2316</td>
<td>6966</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>25</td>
<td>2336</td>
<td>6995</td>
</tr>
</tbody>
</table>

*Evidence of publication bias*

**Conclusion:** Chorioamnionitis cannot be definitively considered a risk factor for BPD.

Hartling, et al., 2011
Comparison of Outcomes for Same Cohort of Patients in Alabama Preterm Birth Study

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic Chorio</td>
<td>61%</td>
<td>73%</td>
<td>*</td>
</tr>
<tr>
<td>Blood Culture+ for Up or Mh</td>
<td>66%</td>
<td>65%</td>
<td>-</td>
</tr>
<tr>
<td><strong>BPD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic Chorio</td>
<td>7%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Blood Culture+ for Up or Mh</td>
<td>27%</td>
<td>10%</td>
<td>*</td>
</tr>
</tbody>
</table>

Chorioamnionitis and BPD

- No Chorioamnionitis
- Mild Chorioamnionitis
- Mod-Severe Chorioamnionitis

BPD Outcomes

Viscardi, et al., 2004
Ventilation and Postnatal Sepsis Increase BPD in Preterm Infants Exposed to Chorioamnionitis

<table>
<thead>
<tr>
<th>Cause</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamnionitis</td>
<td>0.2</td>
<td>0-0.5</td>
</tr>
<tr>
<td>Ventilation &gt;7d and Chorio</td>
<td>3.2</td>
<td>0.9-11</td>
</tr>
<tr>
<td>Postnatal sepsis and Chorio</td>
<td>2.9</td>
<td>1.1-7.4</td>
</tr>
</tbody>
</table>

Will Fetal Infection/Inflammation Cause BPD?

• It depends *almost certainly* on the organism, duration of exposure, intensity of response, and location.

• But, in clinical practice we have no information about
  – Organism(s)
  – Duration of exposure
  – Intensity of maternal/fetal responses
  – Location
Another fetal exposure that decreases RDS but increases BPD:

- Antenatal corticosteroids,
- About 85% of infants <30 wks GA have been exposed to ANS,
- About 50% of infants <30 wks GA have been exposed to chorio,
- Therefore, about 43% exposed to both.
Meta-analysis of Antenatal Corticosteroids

(21 Studies Including 4269 infants)

RDS
- All Infants
- >24h after 1st dose
- 24h - 7d after 1st dose
- 7d after 1st dose

Neonatal Death

Intraventricular Hemorrhage

Necrotizing Enterocolitis

Chronic Lung Disease

Newborn Sepsis - 48h

Roberts & Dalziel, Cochrane Rev., 2006
Antenatal Corticosteroid Effects on BPD

By Gestational Age
(1993-2009; 10,541 infants)

BPD
- 22 wks
- 23 wks
- 24 wks
- 25 wks

Overall

Carlo, et al., JAMA, 2011
Respiratory Outcomes

Meta-Analysis of 10 Trials of REPEATED Antenatal Betamethasone 7 or More Days after an Initial Treatment - 5700 Infants

- BPD
- Mechanical Ventilation
- Surfactant Use
- RDS

Crowther, et al., Cochrane Rev., 2011

• *No BPD benefit*
The Two Major Fetal Exposures Prior to Preterm Delivery

- Antenatal corticosteroids and chorioamnionitis cause “induced” lung maturation

- Maturation associated with an arrest of airspace septation

- Lung phenotype may be a decrease in RDS but an increase in BPD
Risk of BPD or Death Relative to Gestational Age Adjusted Birth Weight Percentiles for 4525 Infants Born at 24-31 Weeks Gestation

Preconditioning to Decrease Injury
Prior Low Exposure to an Insult Attenuates Injury to a Higher Exposure to the Same or Another Insult

<table>
<thead>
<tr>
<th>Preconditioning Low-Grade Insult</th>
<th>Time Interval</th>
<th>Large Insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>At (hours to days)</td>
<td>Hypoxia, Hyperoxia, LPS, Specific Cytokines</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td></td>
<td>Protection</td>
</tr>
<tr>
<td>LPS</td>
<td></td>
<td>Injury</td>
</tr>
</tbody>
</table>

Adapted from Mallard & Hagberg, Sem. Fetal & Neonatal Med., 2007
Disease Tolerance – Fetal/Maternal Unit

Tolerance to damage by pathogen

Direct Damage by Pathogen
- Preterm labor
- Stillbirth
- Neonatal Sepsis
- Organ Injury

Tolerance to damage by immune system

Host resistance mechanisms:
Maternal – innate and acquired
Fetal - ?

Damage from host immune responses:
Maternal – preterm labor
Fetal – cytokines causing brain injury
Antenatal Associations with BPD

- VLBW Delivery
- Chorioamnionitis/inflammation
- Antenatal corticosteroids
- Fetal growth restriction

*The variables are all related to each other – by poorly defined pathways*