The Impact of Premature Delivery on Lung Function and Development

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Objectives

- Discuss embryologic respiratory development, specifically focusing on the lung architecture of infants born at the extremes of prematurity
- Discuss the impact of iatrogenic lung injury on lung function and development
- Discuss current approaches for attenuating the negative effects of supporting an infant’s respiratory needs; specifically: surfactant replacement therapy, non-invasive respiratory support, and oxygen management strategies.
- Discuss the long term consequences of premature delivery and iatrogenic lung injury on future lung function and development
Embyologic Lung Development
Normal Embryologic Development

Embryonic Period
(Conception to Week 6)

Lung bud appears followed by two branches, airway branching begins, pulmonary arteries perfuse developing lung tissue following dividing airways
Normal Embryologic Development

**Pseudoglandular Period**
* (Weeks 7-16)

- Branching continues to the terminal bronchi; muscle, elastic tissue, and early cartilage form along the airways; mucus glands are formed; diaphragm develops
Normal Embryologic Development

Canalicular Period
(Weeks 17-26)

- Airways increase in length and diameter; airways end in blind pouches; few pulmonary capillaries present early in the period; pulmonary capillaries proliferate rapidly toward end of period; formation of alveolar ducts; appearance of Type I and Type II pneumocytes
Normal Embryologic Development

Saccular and Alveolar Period (Weeks 27-Term-Post Term)

- Appearance of alveoli; merging of the alveolar epithelium and the pulmonary capillaries; appearance of mature surfactant; alveoli increase in size and number
Normal Embryologic Development
The Role of Fetal Lung Fluid

- Normal breathing movements and an adequate balance of fetal lung fluid is necessary for normal fetal lung growth and development.
- Fetal breathing movements are necessary to maintain sufficient pressure within the airways and it is thought to possibly stimulate lung growth.
The Role of Fetal Lung Fluid

Polyhydramnios – abnormally large amounts of fluid, indicative of a problem with the swallowing mechanism of the fetus
- CNS malformations
- Orogastric malformations
- Trisomy 21, CHD, IDM

Oligohydramnios – scant or decreased amount of amniotic fluid, usually associated with a defect of the urinary system of the fetus. Inadequate amniotic fluid can lead to:
- Contractures of the limbs
- Clubbing of hands and feet
- Hypoplastic lungs
Factors that Impact Lung Function and Development
Infection

- It is estimated that between 50-80% of preterm births are associated with infection or inflammation of the uterus.

- Fetal exposure to the effects of chorioamnionitis has been shown to decrease the incidence of RDS, however, there is an increased risk of developing chronic lung disease with increased levels of pulmonary inflammation markers.

- Studies done in animal models have shown that chorioamnionitis alters alveolar development and primes the preterm lung for further injury from post-natal factors such as post-natal infection, mechanical ventilation, hyperoxia, and patent ductus arteriosis.
Intrauterine Growth Restriction

- Studies have shown that exposure to factors that restrict fetal growth or lead to low birth weight can alter lung development and have later adverse effects on lung function and respiratory health.

- The major causal factors include:
  - Reduced nutrient and oxygen availability
  - Nicotine exposure via maternal tobacco use
  - Preterm birth
The effects of induced, late gestational IUGR timed to coincide with the saccular-alveolar stages of lung development in animal studies has demonstrated:

- A 31% reduction in the number of alveoli at 8 weeks after term birth which persisted into adulthood
- Alveolar enlargement at 8 weeks and also into adulthood
- The inter-alveolar walls were thicker both at 8 weeks (by 73%) and into adulthood (by 47%)
- The alveolar blood-gas barrier was 47% thicker in IUGR fetuses and 43% thicker in adults
Studies indicated that 20-30% of all infants are exposed to components of tobacco smoke before and/or after birth. The effects of maternal smoking on children include:

- An increased risk of respiratory illness
- Decreased lung function
- Alterations in pulmonary mechanics
  - Reduced expiratory airflow
  - An acceleration in the age-related declines in Forced Vital Capacity (FVC) and Forced Expiratory Volume (FEV₁) (indicative of premature aging of the lung)
Maternal Nicotine Exposure

Maternal nicotine exposure (by inhalation, transdermal patches, gums, nasal sprays, or chewing tobacco) leads to:

- Decreased pulmonary elastin
- Decreased numbers of alveoli
- Greater alveoli volumes
- Increased presence of alveolar wall fenestrations
- Decreased surface area available for gas exchange
Preterm Delivery

The effects of preterm delivery on lung function and development:

- Severe preterm birth (23-26 weeks gestation) can have serious pulmonary complications secondary to assisted ventilation and supplemental oxygen and is highly associated with bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD)
Preterm Delivery

Even mild preterm birth is associated with adverse outcomes in terms of future respiratory health despite the decreased need for assisted ventilation

- Infants born at 30 weeks and studied at 40 weeks showed reductions in functional residual capacity (FRC) and lung compliance, impaired gas-exchange, and higher deadspace ventilation
- Infants born at 35 weeks have demonstrated an association with wheezing and reduced expiratory flows in childhood
Altered Development in the Premature Lung

Although alveoli are present in some infants as early as 32 weeks GA, they are not uniformly present until 36 weeks GA.1

*Pictures are artistic renditions of lung development and are designed to emphasize terminal acinus development and not the entire conducting airway system. Adapted from Moore 2008.2
Altered Development in the Premature Lung

Lung Volume\(^3\) (mL)

<table>
<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>34 weeks’ GA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Term</strong></td>
<td>178 mL</td>
<td>93 mL</td>
</tr>
<tr>
<td><strong>52%</strong></td>
<td>of the lung volume seen in full-term infants</td>
<td></td>
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</tbody>
</table>

Airspace Wall Thickness\(^3\) (µm)

<table>
<thead>
<tr>
<th></th>
<th>Full Term</th>
<th>34 weeks’ GA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Term</strong></td>
<td>12.2 µm</td>
<td>16.4 µm</td>
</tr>
<tr>
<td><strong>34%</strong></td>
<td>THICKER</td>
<td></td>
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</tbody>
</table>

https://www.synagis.com/hcp/sub/premature.aspx
• Thick blood gas barrier
• Low compliance
• Immature epithelial cells
• Low surfactant levels
• Small area for gas exchange
• Poorly vascularized
• High resistance to blood flow

• Thin blood gas barrier
• Highly compliant
• Mature epithelial cells
• Adequate surfactant
• Large area for gas exchange
• Highly vascular
• Low resistance to blood flow
Iatrogenic Lung Injury

![Graph showing volume and pressure (PIP – PEEP)]
Ventilator Induced Lung Injury

138 DAY PRETERM LAMB (TERM = 150 DAYS)

Unventilated

Ventilated for 24 hr
Ventilator Induced Lung Injury

Mechanical ventilation, used for the purpose of supporting respiration or establishing FRC, can sometimes worsen lung conditions by:

- Altering fluid balance
- Increasing endothelial and epithelial permeability
- Causing severe lung damage

Mechanisms of ventilator induced lung injury include:

- Ventilation of the surfactant deficient lung with collapsed alveoli causing shear stress (atelectrauma)
- The use of high tidal volumes to expand alveoli (volutrauma)
- Damage to the lung from excessive pressure changes (barotrauma)
- Pulmonary inflammation leading to leukocyte infiltration and the production of inflammatory mediators (biotrauma)
Oxygen Induced Lung Injury

Newborn Mouse Lungs after 4 weeks exposure to 21% or 85% $O_2$
Excessive fluid volume can lead to increased interstitial fluid in the lung which can interfere with lung compliance and gas exchange resulting in an increased need for respiratory support and subsequent lung injury.

Fluid overload may also contribute to the persistent PDA which results in decreased lung compliance due to increased pulmonary blood flow.

The incidence of CLD and/or death is significantly lower in extremely preterm infants if they lose weight in the first 10 days of life.

Attempts to decrease lung fluid with diuretics may have beneficial effects on lung function and long-term respiratory outcome.
Strategies for Attenuating Lung Injury
Antenatal Steroids

- Stimulates fetal lung maturation
- Decreases the incidence and mortality from intracranial hemorrhage in premature infants
- Given when premature birth between 24 – 34 weeks gestation is expected within 7 days
- Has been shown to decrease the:
  - Incidence of RDS
  - Need for mechanical ventilation
  - Need for surfactant
  - Incidence of BPD
Surfactant

- Found on the alveolar wall, functions to lower surface tension forces
- Appearance coincides with the development of Type II pneumocytes
  - canalicular period 17 – 26 weeks gestation
- Composed of phospholipids, neutral lipids, and proteins
  - Phosphatidylcholine (PC – also called lecithin) makes up the majority weight of surfactant
  - Phosphatidylglycerol (PG) appears around 35 - 36 weeks gestation (mature surfactant) – most reliable indicator of lung maturity
Surfactant Replacement Therapy

- **Rescue** vs. **Prophylactic** surfactant administration
- Exogenous Surfactant Preparations
Vitamin A Supplementation

- Vitamin A is necessary for normal lung growth and maintaining the integrity of respiratory tract epithelial cells.
- Preterm infants have a low vitamin A status at birth and this has been associated with an increased risk of developing chronic lung disease.
- Vitamin A supplementation has been associated with:
  - A reduction in death
  - Oxygen requirement at one month of age
  - Oxygen requirements among survivors at 36 weeks’ PCA
- Information on long-term neurodevelopmental status suggests no evidence of either benefit or harm from the intervention.
Nutrition

- Extremely low birth weight infants are at risk for multiple nutritional deficiencies
- Infants with chronic lung disease are at high risk for growth restriction, delayed bone mass accretion, and delayed catch-up growth
- Early nutrition may be critical to recovery and promotion of optimal growth
The incidence of chronic lung disease and/or death is significantly lower in extremely preterm infants if they lose weight in the first 10 days of life.

Caloric density of feeds may need to be increased to promote proper growth.

Although diuretic therapy has been shown to improve pulmonary mechanics, there is little evidence that the long-term use of diuretics improves clinical outcomes in infants with chronic lung disease.
Oxygen Management Strategies

• Tighter control of oxygen therapy is indicated – especially in the first few weeks of life

• Learn to tolerate lower saturation ranges:
  • For infants <32 weeks PCA → 88 – 94%
  • For infants >32 weeks PCA → 92 – 96%*

• Attempt to decrease the fluctuations of PaO₂ by immediately adjusting FiO₂ in SMALLER increments to accommodate small increases or decreases in pulse oximetry readings
Ventilation Strategies

- **Avoiding intubation and mechanical ventilation when you can:**
  - High Flow Nasal Cannula
  - Nasal CPAP
  - Non-invasive ventilation/ bi-level pressure support

- **Gentle ventilation strategies when you can’t:**
  - Permissive hypercapnia
  - Low tidal volume ventilation
  - HFOV vs. conventional ventilation
  - Strict oxygen management guidelines
Retrospective Cohort Study
Group 1 - born January 2001-June 2002
Group 2 - born July 2004-December 2005
Inclusion criteria
- Less than 1000 grams (ELBW)
- Offered resuscitation
- AGA
- Inborn
- No congenital malformations
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group 1 N=87</th>
<th>Group 2 N=78</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49.4%</td>
<td>56.4%</td>
</tr>
<tr>
<td>Male</td>
<td>50.6%</td>
<td>43.6%</td>
</tr>
<tr>
<td><strong>GA</strong></td>
<td>25.4 w 1.5</td>
<td>25.7 w 1.4</td>
</tr>
<tr>
<td><strong>BWT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects</td>
<td>742 g 125</td>
<td>786 g 120</td>
</tr>
<tr>
<td>Survivors</td>
<td>759 g 121</td>
<td>797 g 116</td>
</tr>
<tr>
<td><strong>PNC</strong></td>
<td>89.7%</td>
<td>94.4%</td>
</tr>
<tr>
<td><strong>Chorio</strong></td>
<td>14.9%</td>
<td>16.9%</td>
</tr>
<tr>
<td><strong>PIH</strong></td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Multiples</strong></td>
<td>28.7%</td>
<td>26.8%</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>36.8%</td>
<td>26.8%</td>
</tr>
<tr>
<td>C/S</td>
<td>63.2%</td>
<td>73.2%</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>80.5%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>13 (15%)</td>
<td>7 (9%)</td>
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</table>

*p<0.05*
Incidence of BPD and Comparison to Neonatal Network

Group 1
Group 2
NICHD

<table>
<thead>
<tr>
<th>Severity</th>
<th>Group 1</th>
<th>Group 2</th>
<th>NICHD</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>16</td>
<td>47</td>
<td>23</td>
</tr>
<tr>
<td>Mild</td>
<td>41</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Moderate</td>
<td>13</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Severe</td>
<td>29</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
</tbody>
</table>
Other Outcomes

<table>
<thead>
<tr>
<th>Intervention or Diagnosis</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
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<tbody>
<tr>
<td>Pressor support during first 24 hrs</td>
<td>39.1%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Steroid Usage</td>
<td>37%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Home Oxygen</td>
<td>25.7%</td>
<td>9%</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3.8%</td>
<td>4.2%</td>
</tr>
<tr>
<td>+Sputum cultures</td>
<td>38.8%</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

p<0.01
Infants are being exposed to significantly less oxygen and fewer days on the ventilator.

Infants are receiving fewer doses of surfactant and postnatal steroids and fewer are going home on oxygen.

Decreased incidence of moderate and severe BPD and a 15% reduction in BPD by previous criteria.

Continuous CPAP for the first 24-48 hours is protective against the development of BPD.

Prophylactic surfactant protects against the need for future intubation.
# Modern Diagnostic Criteria for BPD

<table>
<thead>
<tr>
<th>Classification of BPD</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Oxygen requirement at $\geq 28$ days of life, but not at 36 weeks PCA</td>
</tr>
<tr>
<td>Moderate</td>
<td>Less than 30% oxygen requirement at 36 weeks PCA</td>
</tr>
<tr>
<td>Severe</td>
<td>$\geq 30%$ oxygen requirement or IMV at 36 weeks PCA</td>
</tr>
</tbody>
</table>
Respiratory Outcomes 2009

Infants 401-1500g or 22-29 wks GA

<table>
<thead>
<tr>
<th>Condition</th>
<th>UTMB</th>
<th>VON</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>0.909</td>
<td>0.732</td>
</tr>
<tr>
<td>Oxygen at 28 Days</td>
<td>0.449</td>
<td>0.54</td>
</tr>
<tr>
<td>Oxygen at 36 Weeks</td>
<td>0.284</td>
<td>0.362</td>
</tr>
<tr>
<td>CLD</td>
<td>0.204</td>
<td>0.295</td>
</tr>
<tr>
<td>CLD in infants &lt;33 Weeks</td>
<td>0.213</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Respiratory Outcomes 2010

Infants 401-1500g or 22-29 wks GA

RDS
- UTMB: 87.50%
- VON: 73.60%

Oxygen at 28 Days
- UTMB: 29.80%
- VON: 52.80%

Oxygen at 36 Weeks
- UTMB: 17.90%
- VON: 35.00%

CLD
- UTMB: 13.80%
- VON: 29.10%

CLD in infants <33 Weeks
- UTMB: 13.60%
- VON: 30.70%
Respiratory Outcomes 2011

Infants 401-1500g or 22-29 wks GA

- RDS: 73.60% (VON) vs. 82.50% (UTMB)
- Oxygen at 28 Days: 52.80% (VON) vs. 34.10% (UTMB)
- Oxygen at 36 Weeks: 35.00% (VON) vs. 19.40% (UTMB)
- CLD: 29.10% (VON) vs. 16.90% (UTMB)
- CLD in infants <33 Weeks: 30.70% (VON) vs. 15.40% (UTMB)

Legend: UTMB - Red, VON - Yellow
The Long Term Pulmonary Sequelae of Infants with BPD
Early Effects

- Infants with bronchopulmonary dysplasia (BPD) are frequently susceptible to respiratory infections in the first 2 years of life.
- Poor growth and delayed development are frequently observed.
  - At 18-22 months' corrected age in extremely low birth weight infants, abnormal growth occurred in 50-60% of infants with BPD.
  - The risk of neurodevelopmental impairment, cerebral palsy, and low IQ more than doubled in infants with severe BPD compared with infants with mild BPD.
- Postnatal infection and/or sepsis, PVL, severe IVH, ventriculomegaly, hearing impairment, and severe ROP are all important confounding variables that can greatly affect an infant's outcome.
Late Effects

- Most adolescents and young adults who had BPD in infancy have some degree of pulmonary dysfunction, consisting of:
  - Airway obstruction
  - Airway hyperreactivity
  - Hyperinflation
Prognosis

- Most sufferers survive infancy, but are prone to growth delay, infections, asthma, neurological and cardiac dysfunction.
- Lung function tends to improve slowly throughout childhood, but spirometric and radiological evidence of impaired function/damage usually persists.
- The first 2 years are the 'danger' period for airways disease.
- Affected infants can remain oxygen-dependent for many months and frequently require hospital readmission in the first 2 years after birth.
Prognosis

- Infants with persistent right ventricular hypertrophy or pulmonary hypertension unresponsive to oxygen supplementation carry a worse prognosis.
- The most severely affected may remain symptomatic and have evidence of airway obstruction even as adults.
Questions???
• Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Cochrane Database of Systematic Reviews 2007, Issue 4.