Extracorporeal Support of the Premature Infant (ESPI) – The Artificial Uterus/Placenta
**Acute Complications of prematurity:**
- Retinopathy of prematurity
- Intraventricular hemorrhage
- Developmental delay/Cerebral palsy
- Respiratory insufficiency/CLD
- Patent ductus arteriosus
- Necrotizing enterocolitis
- Hyperbilirubinemia
- Neonatal sepsis
Under the current SoC, extreme prematurity is associated with high mortality and morbidity rates.

- Around 1% of all infants (~30K) born each year are born at 28 weeks or younger
- Both mortality and morbidity are significant concerns

**TARGET POPULATION – 23-26 Weeks Gestation**
Rationale for ESPI

Development of an extra-corporeal *physiologic* fetal support system would abrogate the deleterious effects of premature birth by allowing normal organ maturation.

**Initial Goal**—3 weeks of support to reach milestones with improved mortality/morbidity.

**OBJECTIVES**

- Maintain fetal circulation and fetal PaO₂
- Mimic the sterile intrauterine environment
- Abrogate the need for gas-based lung ventilation
- Allow normal fetal breathing and swallowing (fluid based)
- Support ongoing growth and organ development
History of ESPI

1960’s – UA/UV cannulation, pump assisted, Bubble oxygenators – 40 min – 2 days
2000’s – Mychaliska – Initially pumpless, fluid bath, UA/UV – now pumped VV – ECMO, fluid filled/clamped ET tube – 1 week

All limited by progressive cardiac failure, sepsis, inability to transition from ESPI support

Pumpless ESPI systems – 5 studies - minutes to 29 hours
All limited by cardiac failure

- Fetal heart extremely sensitive to pre-load or afterload imbalance (high resistance oxygenators, pumped circuits)
- Infection is a major limitation of fluid environments
- UA/UV – challenging due to spasm, vascular integrity
Components of ESPI

Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

“Amniotic fluid” environment

Open aquarium, Continuous fluid circulation, Micropore filters

23 – 108 hours (5 animals 120-140 days GA)

Evolution of cannula placement and design

Carotid artery/Jugular vein cannulation (standard ECMO cannulas)

Remarkable hemodynamic Stability

Limited by sepsis/cannula dislodgement

Human (premie) TPN, fluid and Systemic antibiotics, PGE2, narcotic Sedation, heparin
Components of ESPI

**Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit**

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

**“Amniotic fluid” environment**

Semi-closed plexiglass tank, Continuous fluid exchange, parallel UV light chamber

Sheep fetal TPN, fluid and systemic antibiotics, PGE2, Propofol sedation, low or no heparin

**Evolution of cannula placement and design**

Carotid artery/Jugular vein cannulation (Modified ECMO cannulas)

- 348 ± 93 hours (209-480 hrs, 5 animals – 120-125 days GA)
- Hemodynamic/metabolic stability,
- Improved but still limited by sepsis 3/5 animals, 1 survivor
Development of the “Biobag”

- Open sided design, adjustable size
- Adjustable number, size, and configuration of ports
- Metallocene polyethylene film – silver impregnated
- Once sealed, completely closed system, efficiencies of flow and volume.
- Translucent and sonolucent

The Problem of Sepsis
Pre-Clinical Goals of ESPI

Application of ESPI to earlier gestational age fetuses - Developmental Equivalence to Human 22 – 26 week fetus

**HUMAN LUNG DEVELOPMENT**
- Week 1-6
- Week 7-16
- Week 17-26
- Week 27-32
- Week 32-36

**LAMB LUNG DEVELOPMENT**
- Day 0-40
- Day 40-80
- Day 80-120
- Day 120-148

(Human) 22- 26 weeks = (Lamb) 110 – 120 days
Application of ESPI to earlier gestational age fetuses -

Problem – Development of hydrops

Oxygenator perfusion pressure/Flow directly related to -

Carotid arterial pressure - SVC pressure

Decreasing GA → Jugular/SVC venous return

Image of a fetal circulatory system with labels for various vessels and structures.
Components of ESPI

Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

“Amniotic fluid” environment

Closed Biobag system, Continuous fluid exchange

Sheep fetal TPN, systemic antibiotics, PGE2, Propofol sedation, low or no heparin

Evolution of cannula placement and design

Carotid artery/Umbilical vein cannulation (Modified ECMO cannulas)
Hemodynamic/metabolic Stability on ESPI

GA – 108 – 113 Days – 5 animals/20 – 26 days on ESPI
Hemodynamic/metabolic Stability on ESPI

<table>
<thead>
<tr>
<th></th>
<th>In utero (GA 125 d)</th>
<th>Lamb 1</th>
<th>Lamb 2</th>
<th>Lamb 3</th>
<th>Lamb 4</th>
<th>Lamb 5</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb (g/dl)</td>
<td>8.9</td>
<td>13.2</td>
<td>12.1</td>
<td>11.6</td>
<td>11.7</td>
<td>11.5</td>
<td>12.0</td>
</tr>
<tr>
<td>&quot;Circuit&quot; flow (ml/kg*min)</td>
<td>200 (umbil. flow)</td>
<td>76.8</td>
<td>83.2</td>
<td>83.1</td>
<td>94.0</td>
<td>117.8</td>
<td>91.0</td>
</tr>
<tr>
<td>Total O₂ delivery (ml/kg*min)</td>
<td>19.6</td>
<td>14.3</td>
<td>13.7</td>
<td>13.5</td>
<td>17.0</td>
<td>19.2</td>
<td>15.5</td>
</tr>
<tr>
<td>Total O₂ consumption (ml/kg*min)</td>
<td>6.7</td>
<td>6.9</td>
<td>6.2</td>
<td>5.0</td>
<td>5.5</td>
<td>8.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Total O₂ extraction (%)</td>
<td>34.2</td>
<td>48.0</td>
<td>45.5</td>
<td>37.8</td>
<td>33.4</td>
<td>44.2</td>
<td>41.8</td>
</tr>
<tr>
<td>Carotid P&lt;sub&gt;O2&lt;/sub&gt; (mm Hg)</td>
<td>23.1</td>
<td>31.2</td>
<td>34.5</td>
<td>36.9</td>
<td>42.6</td>
<td>34.1</td>
<td>35.9</td>
</tr>
<tr>
<td>Carotid O₂ sat (%)</td>
<td>62.0</td>
<td>52.7</td>
<td>56.5</td>
<td>62.6</td>
<td>68.5</td>
<td>57.6</td>
<td>59.6</td>
</tr>
<tr>
<td>Carotid O₂ content (ml O₂/dl blood)</td>
<td>7.5</td>
<td>9.5</td>
<td>9.3</td>
<td>9.8</td>
<td>10.9</td>
<td>9.0</td>
<td>9.7</td>
</tr>
<tr>
<td>Plasma lactate (mmol/L)</td>
<td>1.8</td>
<td>1.5</td>
<td>0.7</td>
<td>0.5</td>
<td>0.4</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>
• 5 successful 3 weeks runs on BioBag ESPI system
• Evidence of appropriate maturation with secondary septations, well-formed alveolae, wide airspaces
• No evidence of infection or inflammation
• Normal radial alveolar count (RAC), morphometrics, Surfactant staining
Components of ESPI

- Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit
  - Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

- “Amniotic fluid” environment
  - Closed Biobag system, Continuous fluid exchange
    - Sheep fetal TPN, systemic antibiotics, PGE2, Propofol sedation, low or no heparin

- Evolution of cannula placement and design
  - Umbilical Artery (2)/Umbilical vein cannulation/New cannula design
Maintenance of the Fetal Circulation

*Ductus Arteriosus*
<table>
<thead>
<tr>
<th><strong>Ductus Venosus</strong></th>
<th><strong>Foramen Ovale</strong></th>
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**Maintenance of the Fetal Circulation**
Concerns related to cerebral blood flow/brain development

Subphysiologic "placental" perfusion

70 – 100 ml/kg/min vs. 150-200 ml/kg/min
Compensations to achieve normal O$_2$ delivery

\[ \text{Hb} \quad \text{Post membrane pO}_2 \]
\[ \text{O}_2 \text{ Consumption (sedation)} \]

Issues related to cannula dislodgment and removal
Achievement of Normal Fetal Circulation

UA/UV Cannulation

- Ongoing studies – 2 UAs, 1 UV, 3 lambs – 105-108 d GA – 28 day Runs. 1 lamb – severe TOF -28 d

- Observations
  - Circuit flows to 150-200 ml/kg/min
  - Pre-membrane pressures
    - With autoregulation across the post membrane UV and DV
  - Normal $O_2$ delivery and $O_2$ Consumption (nutrition) without compensations
  - Reduced concern regarding cannula dislodgements, Reduced sedation requirements
Hemodynamic/metabolic Stability on ESPI

GA – 108 – 113 Days – 5 animals/20 – 26 days on ESPI
Hemodynamic/metabolic Stability on ESPI

GA – 105 – 107 Days – 3 animals/28 days on ESPI
ESPI Applications

Extreme Prematurity
- Initially 23 – 24 wk extreme premature infant

Transitional Applications
- CDH – EXIT to ESPI at 35 wks - 3-4 weeks of ESPI prior to gas ventilation – Pharmacologic treatment of pulmonary HTN +/- lung growth strategies, diaphragmatic hernia repair
- Fetal Growth Restriction
- Support of infants with congenital heart disease for organ/brain maturation prior to cardiac repair
- Gene therapy/cell therapy applications?