Fetal Therapy

Definitions:

• Fetal intervention
  • Non-invasive (time, mode of delivery)
  • Minimally invasive therapy
  • Invasive therapy
    • Fetal surgery
    • EXIT procedure
Fetal Surgery

Problems and research:

• Major *maternal* surgery (laparotomy)
• Hysterotomy
  • Bleeding ++
  • Membrane integrity/rupture/separation
  • Intraoperative contractions
Fetal Surgery

Problems and research:

• Fragile fetus
  • Dehydration
  • Hypothermia (1°C per 5 min of surgery)
  • Direct fetal trauma
  • Cord manipulation
  • Complex operations!

• Postoperative tocolysis and labor!
Fetal Surgery

Solutions and research:

- Back-biting hysterotomy clamps
- Staplers
  - Absorbable staples
- Anesthesia
- Tocolysis
  - Halogenated gases
  - Postoperative: ideal agent?
Fetal Surgery

Animal models:

- Fetal rabbit
  - Basic physiologic principles
- Fetal lamb
  - Quiescent uterus
  - Tolerant fetus
  - Long gestation (145 d)
Fetal Surgery

Animal models:

- Non-human primate
  - More realistic
  - Sensitive uterus
  - Last step before clinical application

- Rhesus monkey
- Baboon
Fetal Surgery

Types of operations:

• Lower urinary tract obstruction (LUTO)
  • Pulmonary hypoplasia prevention
• Congenital diaphragmatic hernia (CDH)
  • Pulmonary hypoplasia prevention
• Large CCAM
  • Pulmonary hypoplasia prevention
  • Avoid/reverse fetal hydrops
• Sacrococcygeal teratoma
  • Avoid fetal hydrops and maternal ecclampsia
Fetal Surgery

Results:

• 100% preterm labor
• High fetal mortality (condition-specific)
  • CDH: 14% survival
  • SCT: 0% survival
  • Vesicostomy: 75% renal failure
  • CCAM: 60% survival
Fetal Surgery

Results:

• Maternal complications
  • Blood transfusion 12%
  • Pulmonary edema 12-16%
  • Tocolysis (average duration) 90.0 hours
  • ICU stay (average stay) 9.6 d
  • Mandatory subsequent C/S
## Open fetal surgery

### Maternal complications:

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm labor</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>Transfusion</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Amniotic fluid leak</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Mirror syndrome</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Harrison MR, SPO 1995*
Open fetal surgery

Results: the MOMS trial (N=78)

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamniotic separation</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Delivery &gt; 36-37 wk</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Intact hysterotomy wound</td>
<td>49</td>
<td>64</td>
</tr>
</tbody>
</table>

Adzick NS et al, 2011
Fetal Surgery

Conditions that have to be met:

- Correct prenatal diagnosis
- Correct differential diagnosis
- Known natural history
- Condition lethal if left untreated
- No available postnatal treatment
- Fetal operation feasible
Fetal Surgery

So... What’s left?

- Spina bifida
  - MOMS trial
- Diaphragmatic hernia
  - Open repair: results worse than postnatal R/
  - Endoscopic repair: tracheal occlusion trial
- CCAM, SCT
  - Only extreme, exceptional cases
- Urinary tract obstruction
  - Only percutaneous, sometimes
- TTTS, Acardiac twin
Laser Ablation for TTTS

Technique:

- Minimally invasive surgery
- Percutaneous vs. open endoscopy vs. laparotomy
- Local vs. regional vs. general anesthesia
- Access and exit techniques

Risks:

- Chorioamnionitis
- Preterm labor
- Membrane rupture/PPROM
- Amniotic leak
- Bleeding
Laser Ablation for TTTS

Instrument: 1 port, Mini-Endoscope

1.9 mm diameter
Low-flow irrigation

Sheath 3 mm diameter

400 μ laser

Instrument dimensions compared to a penny.
Laser Ablation for TTTS

The operating room
Twin-to-twin Transfusion - Laser

Do the patients survive?

Survival

Postoperative days

Recipient
Donor

Car SR et al
SMFM annual meeting 2006
Congenital Diaphragmatic Hernia

One-Slide Background

- Herniated viscera compress the lungs
- Hypoplastic lungs function poorly
  - Decades ago: 80% mortality at birth
- Prenatal repair of the hernia too invasive
  - 14% survival
Congenital Diaphragmatic Hernia

One-Slide Background

• Fetal tracheal occlusion makes the lungs grow
  • Works great in animal models
Late Lung Maturation

- Fluid excretion
- STRETCH
- C1-
- PGE2 secretion
- DNA synthesis
- PL synthesis
- SP synthesis
- MAP kinase

Fibroblast

- cAMP
- PTHrP
- IL-6,11
- TG uptake and release
- IGF, HGF, KGF, EGF, TGF-β

Type II cell

- TG incorporation
Late Lung Maturation

**Fibroblast**

**Type II cell**

**SPACE-**
**OCCUPYING**
**MASS**

**STRETCH**

**Fluid excretion**

**Cl⁻**

**PGE2 secretion**
Late Lung Maturation

**TRACHEAL OCCLUSION**

**Fibroblast**

- STRETCH
- Fluid excretion
- CL-
- IL-6,11
- TG uptake and release
- TG incorporation
- cAMP
- PTHrP
- DNA synthesis
- PL synthesis
- SP synthesis
- MAP kinase

**Type II cell**

- PGE2 secretion
- IGF, HGF, KGF, EGF, TGF-β
Fetal Surgery

Diaphragmatic hernia

- Tracheoscopy and detachable balloon
- Prenatal surgery ‘no better’ than postnatal treatment
- Moratorium in U.S.
- European experience encouraging
8/3/07 R lung

9/18/07 Tracheal balloon L lung
Now what?

- Late, temporary occlusion works
- Rapid lung growth and proliferation
- Investigational Device Exemption (FDA)
- Three centers in the US:
  - Brown
  - UCSF
  - Baylor
Spina Bifida

Outcome of fetal surgery

First report: Adzick NS et al? Bruner JP et al?
Spina Bifida

Outcome of fetal surgery

First report: Adzick NS et al? Bruner JP et al?
Spina Bifida

Adzick NS et al, 2011
Spina Bifida

Adzick NS et al, 2011
## Spina Bifida: MOMS Trial

### Results (%)

<table>
<thead>
<tr>
<th></th>
<th>Fetal</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt criteria met</td>
<td>65</td>
<td>92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Shunt placed</td>
<td>40</td>
<td>82</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hindbrain herniation</td>
<td>64</td>
<td>96</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baylor Psychomotor</td>
<td>64.0</td>
<td>58.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Walking unassisted</td>
<td>42</td>
<td>21</td>
<td>0.03</td>
</tr>
</tbody>
</table>

## Spina Bifida: MOMS Trial

### Complications (%)

<table>
<thead>
<tr>
<th>Maternal complications</th>
<th>Fetal</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema</td>
<td>6</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>6</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>3</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Uterine wound intact</td>
<td>64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Spina Bifida

Now that the MOMS trial is over

Standard of care?

What about maternal safety?

What about the trial effect?

• Future results may not match the MOMS results
Spina Bifida

Now that the MOMS trial is over

Minimally invasive approach?

(Didn’t work in 2002, but how about now?)
Fetal Surgery Spin-off: The EXIT Procedure

Fig 1. Fetal monitoring options during an EXIT procedure.
EXIT Procedure

Multidisciplinary team:

- Pediatric Anesthesia
- Pediatric Surgery
- Pediatric ENT
- Pediatric Radiology
- Pediatric OR Nurses
- Neonatologists
- Respiratory Therapists
- Neonatology Nurses

- Obstetrical Anesthesia
- Maternal-Fetal Medicine
- OB OR Nurses
Tracheostomy
<table>
<thead>
<tr>
<th>Indications</th>
<th>No.</th>
<th>Gestational Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of tracheal occlusion</td>
<td>13</td>
<td>31.8</td>
</tr>
<tr>
<td>Giant fetal neck mass</td>
<td>13</td>
<td>36.0</td>
</tr>
<tr>
<td>EXIT-to-ECMO</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>Resection of CCAM</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Unilateral pulmonary agenesis</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>Bridge to separation for conjoined twins</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>CHAOS</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Overall</td>
<td>31</td>
<td>34.2</td>
</tr>
</tbody>
</table>

The EXIT Procedure: Experience and Outcome in 31 Cases

By Sarah Bouchard, Mark P. Johnson, Alan W. Flake, Lori J. Howell, Laura B. Myers, N. Scott Adzick, and Timothy M. Crombleholme

Philadelphia, Pennsylvania

Journal of Pediatric Surgery, Vol 37, No 3 (March), 2002: pp 418-426
### Table 2. Duration of Uteroplacental Gas Exchange

<table>
<thead>
<tr>
<th>Indications</th>
<th>Minutes on Uteroplacental Support (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of tracheal occlusion</td>
<td>26.7 ± 6.3 (18-38)</td>
</tr>
<tr>
<td>Giant fetal neck mass</td>
<td>29.2 ± 16.4 (8-54)</td>
</tr>
<tr>
<td>EXIT-to-ECMO</td>
<td>58</td>
</tr>
<tr>
<td>Resection of CCAM</td>
<td>66</td>
</tr>
<tr>
<td>Unilateral pulmonary agenesis</td>
<td>14</td>
</tr>
<tr>
<td>Bridge to separation conjoined twins</td>
<td>43</td>
</tr>
<tr>
<td>CHAOS</td>
<td>25</td>
</tr>
<tr>
<td>Overall</td>
<td>30.3 ± 14.7 (8-66)</td>
</tr>
</tbody>
</table>
Table 1. Indications and Outcome Data for EXIT Procedure

<table>
<thead>
<tr>
<th>Indication for EXIT</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH</td>
<td>45</td>
</tr>
<tr>
<td>Neck mass</td>
<td>5</td>
</tr>
<tr>
<td>CHAOS</td>
<td>2</td>
</tr>
</tbody>
</table>

Outcome data for EXIT procedures

- Survivors: 27 (52%)
- Female:male: 1:2
- Gestational age at birth (wk): $31.95 \pm 2.55$
- Birth weight (g): $1895 \pm 853$
- Maternal blood loss (mL): $970 \pm 510$
- Time on placental support (min): $45 \pm 25$
- Tracheostomy-dependent (n of patients): 6

The Ex Utero Intrapartum Treatment Procedure: Looking Back at the EXIT

By Shinjiro Hirose, Diana L. Farmer, Hanmin Lee, Kerilyn K. Nobuhara, and Michael R. Harrison

San Francisco, California