What’s on the Horizon for Fetal Surgery?

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Professor of Pediatric Surgery
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Texas Fetal Center
Children’s Memorial Hermann Hospital
Definition of Maternal-Fetal Surgery

• Operating on two patients simultaneously where both incur risks
• Benefits to mother probably not medically definable
• Opportunity to correct a surgically-treatable lesion or diminish its sequelaes
Historical Perspectives

• **1982**: First open fetal surgery for obstructive uropathy

• **1981-1994**: All surgeries performed for fetal defects considered lethal
  - Diaphragmatic hernia
  - Cystic adenomatoid malformation
  - Bladder outlet obstruction
  - Sacrococcygeal teratoma
• Overview
• Myelomeningocele
• Twin-twin transfusion
• Discordant anomalies
• TRAP sequence
• Diaphragmatic hernia
• Where are we now?
• Where are we going?
Myelomeingocoele
Normally formed brain

- CEREBRUM
- VENTRICLES
- CEREBELLUM
- Fluid flows from ventricles here
- BRAIN STEM
- SPINAL CORD

Chiari II malformation causing hydrocephalus

- Enlarged ventricles filled with fluid
- Abnormal position of brain blocks fluid flow
Hindbrain Herniation
Mouse model

Stiefel et al. J Neurosurg 2007;106:213-21
Normal sheep spine

Spina bifida @ 75 days
Followed by closure @ 100 days

Spina bifida @ 75 days w/o closure

Historical Perspectives

• 1994: Bruner attempts laparoscopic repair of NTD (4 cases performed before stopping)
• 1998: Tulipan reports open repair at 28-30 weeks gestation in 4 fetuses
  – All with absent hindbrain herniation at birth
  – 2 required ventricular shunts
• 244 open cases to date (170 at VUMC, 52 at CHOP, 12 at UCSF, 10 at UNC)

Am J Obstet Gynecol 1997;176:256-7
Pediatr Neurosurg 1998;29:274-8
Feb 2003 – Dec 2010
$22.5 million
MOMS Inclusion Criteria (maternal)

- Singleton pregnancy
- Gestational age at randomization of 19\(^{0/7}\) to 25\(^{6/7}\) weeks gestation
- Maternal age > 18 years
- Body mass index < 35
- No previous uterine incision in the active uterine segment
- No risk factors for preterm birth (short cervix, history of previous preterm delivery)
MOMS Exclusion Criteria (maternal)

- Insulin-dependent diabetes
- Infection with hepatitis B or C
- HIV infection
- Red cell/platelet alloimmunization
- Unwillingness to accept blood transfusions for religious or other reasons
MOMS Inclusion Criteria (fetal)

- Myelomeningocele defect between levels T1 to S1
- No evidence of kyphosis (curved spine)
- No major fetal anomaly unrelated to the spina bifida
- Normal chromosomes by amniocentesis
## MOMS Outcomes (Maternal)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fetal surgery</th>
<th>Postnatal surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane separation</td>
<td>26%</td>
<td>0%</td>
</tr>
<tr>
<td>Rupture of membranes</td>
<td>46%</td>
<td>8%</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Abruption</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Infection</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased amniotic fluid</td>
<td>21%</td>
<td>4%</td>
</tr>
<tr>
<td>Status of uterine incision at delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very thin</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Partial separation</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

- [UTHealth](https://www.uthealth.edu/)
- [Texas Fetal Center](https://www.texasfetalcenter.org/)
- [Children's Memorial Hermann Hospital](https://www.chmhealth.org/)

[Source](https://www.uthealth.edu/)

The University of Texas Health Science Center at Houston
Medical School
# MOMS Outcomes (Neonatal)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fetal surgery</th>
<th>Postnatal surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gest Age (wks)</strong></td>
<td>34.1 ± 3.1</td>
<td>37.3 ± 1.1</td>
</tr>
<tr>
<td>&lt; 30 wks</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>30 – 34 wks</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>35 – 36 wks</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Birthweight (gms)</strong></td>
<td>2383 ± 688</td>
<td>3039 ± 469</td>
</tr>
<tr>
<td><strong>Respiratory distress syndrome</strong></td>
<td>21%</td>
<td>6%</td>
</tr>
</tbody>
</table>

1 in 5 delivered at term
## MOMS Outcomes (12 months)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fetal surgery</th>
<th>Postnatal surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>68%</td>
<td>98%</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Shunt criteria met</td>
<td>65%</td>
<td>98%</td>
</tr>
<tr>
<td>Shunt placement</td>
<td>40%</td>
<td>82%</td>
</tr>
<tr>
<td>Any hindbrain herniation</td>
<td>64%</td>
<td>96%</td>
</tr>
</tbody>
</table>
## MOMS Outcomes (30 months)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fetal surgery</th>
<th>Postnatal surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley MDI</td>
<td>89.7 ± 14.0</td>
<td>87.3 ± 18.4</td>
</tr>
<tr>
<td>Δ motor/anat level</td>
<td>0.58 ± 1.94</td>
<td>-0.69 ± 1.99</td>
</tr>
<tr>
<td>&gt; 2 levels higher</td>
<td>32%</td>
<td>12%</td>
</tr>
<tr>
<td>Walking independently</td>
<td><strong>42%</strong></td>
<td><strong>21%</strong></td>
</tr>
</tbody>
</table>
## Texas Fetal Center Experience

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Gravidity</th>
<th>GA @ Procedure</th>
<th>Level of Lesion</th>
<th>GA @ Delivery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>G2P1</td>
<td>24 4/7</td>
<td>L1-L2</td>
<td>32 3/7</td>
<td>No shunt at one year</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>G2P0</td>
<td>25</td>
<td>L1-L2</td>
<td>25 4/7</td>
<td>No shunt at 10 mo of age</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>G4P3</td>
<td>22 4/7</td>
<td>L3 – S3</td>
<td>36 4/7</td>
<td>Revision of repair; shunt at 3 weeks of age</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>G7P2</td>
<td>24</td>
<td>L5-S1</td>
<td>30 0/7</td>
<td>No shunt at 38 days, baby doing well at home</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>G3P2</td>
<td>24 1/7</td>
<td>L2-S4</td>
<td>35 0/7</td>
<td>No shunt at 11 days, baby doing well at home</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>G1P0</td>
<td>25 4/7</td>
<td>L2-S3</td>
<td>30</td>
<td>Baby in NICU; shunt at 2 weeks of age</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>G1P0</td>
<td>23 5/7</td>
<td>T12-S5</td>
<td>32 1/7</td>
<td>Delivered on 12/8</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>G2P1</td>
<td>25 5/7</td>
<td>L4-S5</td>
<td>---</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

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**Texas Fetal Center**

Children's Memorial Hermann Hospital
Twin – twin Transfusion Syndrome
Twin-Twin Transfusion Syndrome

**DIAGNOSTIC CRITERIA**

- Like sex
- Single placenta
- Thin dividing membrane (monochorionic)
- Massive hydramnios (> 8 cm vertical pocket) / oligohydramnios (< 2 cm vertical pocket)
- 10% of all monochorionic twins
Monochorionic Twins/
TTTS Staging

Stage 1
Donor MVP <2 cm;
Recipient MVP >8-10 cm

Stage 2
Absent bladder in donor twin;
normal Doppler studies
Monochorionic Twins/
TTTS Staging

Stage 3

Normal

Abnormal

Umbilical Artery

Recipient

Donor

Umbilical Vein

Ductus Venosus

Middle Cerebral Artery
Monochorionic Twins/TTTS Staging

Stage 4

Stage 5
One or both fetuses have died
Monochorionic Twins/
Pathophysiology of TTTS
Laser Photocoagulation
Monochorionic Twins/
Laser vs. Amnio for TTTS

**TABLE 3**  
Meta-analysis of overall survival rate

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>LASER*</th>
<th>AMNIONCUTION*</th>
<th>Weight (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1999</td>
<td>89/146</td>
<td>44/86</td>
<td>36.44%</td>
<td>1.4904 (0.8704 to 2.5522)</td>
</tr>
<tr>
<td>B</td>
<td>2004</td>
<td>81/138</td>
<td>54/136</td>
<td>37.87%</td>
<td>2.1579 (1.3319 to 3.495)</td>
</tr>
<tr>
<td>C</td>
<td>2006</td>
<td>48/62</td>
<td>32/54</td>
<td>13.02%</td>
<td>2.3571 (1.0532 to 5.2757)</td>
</tr>
<tr>
<td>D</td>
<td>2007</td>
<td>89/116</td>
<td>22/42</td>
<td>12.67%</td>
<td>2.0996 (1.4254 to 6.2999)</td>
</tr>
</tbody>
</table>

**META-ANALYSIS:**  
307/462 | 152/318  
Z=4.06; P<0.0001

OR: odds ratio; CI: Confidence Interval  
Test of heterogeneity: Q=2.51; P=0.47; I^2=0%

Monochorionic Twins/ Laser vs. Amnio for TTTS

**Table 4**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>LASER*</th>
<th>AMNIOREDUCTION*</th>
<th>Weight (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1999</td>
<td>3/95</td>
<td>7/51</td>
<td>11.53%</td>
<td>0.4238 (0.1344 to 1.3366)</td>
</tr>
<tr>
<td>B</td>
<td>2004</td>
<td>12/144</td>
<td>41/140</td>
<td>51.51%</td>
<td>0.2195 (0.1097 to 0.4394)</td>
</tr>
<tr>
<td>C</td>
<td>2006</td>
<td>3/62</td>
<td>9/54</td>
<td>12.37%</td>
<td>0.2542 (0.0851 to 0.9935)</td>
</tr>
<tr>
<td>D</td>
<td>2007</td>
<td>12/101</td>
<td>14/36</td>
<td>24.58%</td>
<td>0.2119 (0.086 to 0.5218)</td>
</tr>
</tbody>
</table>

META-ANALYSIS: 33/402  71/281  

Z = 5.91; P < 0.0001

* number of infants death / total number of infants
OR: odds ratio; CI: confidence interval
Test of heterogeneity: Q = 1.07; P = 0.76; I² = 0%

## Monochorionic Twins
### TTTS Neurologic Outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Percent follow-up</th>
<th>Age @ follow-up</th>
<th>Normal</th>
<th>Minor abnormal</th>
<th>Major abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salomon</td>
<td>73</td>
<td>96%</td>
<td>60 mo</td>
<td>84%</td>
<td>—</td>
<td>16%</td>
</tr>
<tr>
<td>Rossi</td>
<td>895</td>
<td>96.8%</td>
<td>Birth</td>
<td>* 94%</td>
<td>—</td>
<td>* 6%</td>
</tr>
<tr>
<td></td>
<td>1255</td>
<td>96.8%</td>
<td>6-48 mo</td>
<td># 89%</td>
<td>—</td>
<td># 11%</td>
</tr>
</tbody>
</table>

- No difference between donor and recipient

Rossi et al. Obstet Gynecol 2011;118:1145-50*
Monochorionic Twins
Learning Curve of Laser

Discordant Anomalies in Monochorionic Gestations
Monochorionic Twins
Risk of Single Demise

Risk of in-utero death of affected twin
– Old theory of “bad humors” crossing to the live twin discounted
– Acute hemodynamic changes the more likely etiology
– No benefit from acute delivery
– 15% of cases associated with IUFD of co-twin
  • ↑ 5X over dichorionic twins
– 26% of survivors with neurologic sequelae
  • ↑ 5X over dichorionic twins

Bipolar Umbilical Cord Occlusion
Starburst™ SDE RFA Needle

- Length: 12 cm
- Diameter: 2 cm
- Gauge: 17 g

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Texas Fetal Center

Children's Memorial Hermann Hospital
## RFA vs. Bipolar

<table>
<thead>
<tr>
<th></th>
<th>RFA (N = 17)</th>
<th>Bipolar (N = 34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operative time</strong></td>
<td>31.8 ± 22</td>
<td>29.8 ± 22</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Type of anesthesia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV sedation</td>
<td>17</td>
<td>23</td>
<td>0.03</td>
</tr>
<tr>
<td>Spinal</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>General with ETT</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>PPROM</strong></td>
<td>1 (6%)</td>
<td>8 (24%)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Weeks gained</strong></td>
<td>13.8 ± 6.8</td>
<td>13.0 ± 5.6</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>GA @ delivery</strong></td>
<td>34.4 ± 5</td>
<td>33.9 ± 5</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Survival (O/E)</strong></td>
<td>17/19 (90%)</td>
<td>31/36 (86%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Roman et al. Ultrasound Obstet Gynecol 2010;36:37-41*
Twin Reversed Arterial Perfusion Syndrome (TRAP)
Acardius anceps
83% Survival

Lee et al. Am J Obstet Gynecol 2008;199:S4
Diaphragmatic Hernia
UNC CHAPEL HILL
ATL

Map 3
170dB/C 4
Persist Off
2D Opt:HSCT
Fr Rate:Surv
SonoCT™

BW 0  Pg 0

Heart

R
RT LUNG

L
LT LUNG
Diaphragmatic Hernia  (LHR Ratio)

LHR = AP X TRANS of contralateral lung
Head circumference (mm)
Diaphragmatic Hernia (LHR Ratio)

<table>
<thead>
<tr>
<th>LHR</th>
<th>Liver</th>
<th>N</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.4</td>
<td>NA</td>
<td>10</td>
<td>80%</td>
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</table>

Deprest et al. Semin Perinatol 2005;29:94-103
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<thead>
<tr>
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<tr>
<td>&gt; 1.4</td>
<td>NA</td>
<td>10</td>
<td>80%</td>
</tr>
<tr>
<td>1.0 – 1.4</td>
<td>↓</td>
<td>7</td>
<td>71%</td>
</tr>
</tbody>
</table>

Deprest et al. Semin Perinatol 2005;29:94-103
## Diaphragmatic Hernia (LHR Ratio)

<table>
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<td>10</td>
<td>80%</td>
</tr>
<tr>
<td>1.0 – 1.4</td>
<td>↓</td>
<td>7</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>7</td>
<td>57%</td>
</tr>
</tbody>
</table>

Deprest et al. Semin Perinatol 2005:29:94-103
## Diaphragmatic Hernia (LHR Ratio)

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<td>10</td>
<td>80%</td>
</tr>
<tr>
<td>1.0 - 1.4</td>
<td>↓</td>
<td>7</td>
<td>71%</td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>↓</td>
<td>12</td>
<td>42%</td>
</tr>
</tbody>
</table>

Deprest et al. Semin Perinatol 2005;29:94-103
## Diaphragmatic Hernia (LHR Ratio)

<table>
<thead>
<tr>
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<td>7</td>
<td>71%</td>
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<td>↑</td>
<td>12</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>17</td>
<td>6%</td>
</tr>
</tbody>
</table>

Deprest et al. Semin Perinatol 2005:29:94-103
Diaphragmatic Hernia

Treatment

- 1986: First attempt at open fetal surgery
- 1986 – 1993: “Liver up” not amenable to open repair due to kinking of umbilical vein w/repair
- 1993 – 1996: NIH sponsored trial for open repair
Survival (% of infants) vs. Age (days)

LHR >0.90 (n=15)

LHR ≤0.90 (n=9)
Fetoscopic treatment of diaphragmatic hernia
Diaphragmatic Hernia

- 26 – 28 weeks’ gestation
- General maternal anesthesia
- IM fetal pancuronium, atropine, fentanyl
- 1.2 mm scope; 0.8 ml balloon
- Remove at 34 weeks

Deprest et al. Semin Perinatol 2005;29:94-103
Diaphragmatic Hernia

- 210 cases
- 47% PPROM
  - median: 30 days post-procedure
  - within 3 wks of procedure: 17%
  - Gest age at delivery: 35.3wks (30% @ < 34 wks)
- 10 neonatal deaths related to balloon removal
- Overall survival
  - L sided: 24% → 49%
  - R sided: 0% → 35%

Jani et al. Ultrasound Obstet Gynecol 2009;34:304-10
Diaphragmatic Hernia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FETO</th>
<th>Controls</th>
<th>P or RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>20</td>
<td>21</td>
<td>----</td>
</tr>
<tr>
<td>GA @ delivery (wks)</td>
<td>35.6 ± 2.4</td>
<td>37.4 ± 1.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Survival to 6 mo</td>
<td>50%</td>
<td>4.8%</td>
<td>10.5 (1.5 – 74.7)</td>
</tr>
<tr>
<td>Survival to 6 mo (received treatment)</td>
<td>52.9%</td>
<td>5.3%</td>
<td>10.0 (1.4 – 70.6)</td>
</tr>
</tbody>
</table>

Selection of Patients

100 antenatal diagnoses

13 Right sided

87 Left sided

30 with LHR < 1.0

20 with liver up
Current Therapy Offered

- EXIT procedure
- Open fetal surgery for certain lesions (NTD, rarely CCAM & sacrococcygeal teratoma)
- Laser for TTTS
- Selective reduction for discordant fetal anomalies in MC twins
- Shunt placement (thoracic/urinary)
- Intrauterine transfusions
Future Therapy Offered

- Tracheal balloon for diaphragmatic hernia
- Invasive fetal cardiac therapy
- Fetal stem cell transplant
- Robotic surgery for NTD or gastroschisis?