Fetal Intervention Update 2017

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Disclosures

Receive royalty payments for authorship of the chapters on twin twin transfusion syndrome in UpToDate®

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 sequelae

Objectives

• Review current clinical procedures and potential future maternal fetal interventions
  • Twin twin transfusion (TTTS)
  • Fetal myelomeningocele (fMMC)
  • Fetal diaphragm hernia ~ FETO

Complicated Monochorionic Multifetal Pregnancies

Outcome of MCDA twin gestations in the era of invasive fetal therapy

<table>
<thead>
<tr>
<th>Survival</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin live births</td>
<td>172</td>
<td>85%</td>
</tr>
<tr>
<td>Singleton</td>
<td>15</td>
<td>7%</td>
</tr>
<tr>
<td>Double demise</td>
<td>15</td>
<td>7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TTTS</td>
<td>18</td>
<td>9%</td>
</tr>
<tr>
<td>sIUGR</td>
<td>30</td>
<td>15%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Losses</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>11%</td>
<td>42%</td>
</tr>
<tr>
<td>&lt; 24 weeks</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>≥ 24 weeks</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

Hidden Mortality of MC Twins
Extra loss in MC twins is due to complications placental anastomoses

Lew et al., 2004
Diagnosis

"There is **NO** diagnosis of twins.

The only diagnosis is a monochorionic or dichorionic twin gestation.

This should be written in capital **red** letters on the front of the chart at 8 - 10 weeks".

Monochorionic Twin Pregnancy

Interfetal Anastomoses

- Discordance in AV/VA Flow
- Discordance in Placental Territories
- Discordance in Fetal Malformations
- Chronic Unbalanced transfusion
- TOPS TAPS
- High risk of hemodynamic accident
- High risk of intrauterine fetal death
- Acute feto-feto transfusion

Monochorionic Multifetal

**Acute Twin Twin Transfusion**

- **Perimortem TTTS**
  - Transfusion from surviving twin into dead fetus
  - 18-34% brain injury
  - 15% co-twin demise
  - Optimal treatment not known
- **Acute Perinatal TTTS – Intrapartum**
  - 2-5%
  - Acute shifts in blood pressure differences
  - Discordant hemoglobin values > 5g/dL
  - Treatment
    - Donor – O2 and volume expansion – transfuse w/ RBC
    - Recipient – partial exchange transfusion
Chronic Twin-Twin Transfusion Syndrome

Twin Oligohydramnios Polyhydramnios Syndrome TOPS

Monochorionic Twins
Pathophysiology of TTTS

Net transfer of blood or other vasoactive substance from one fetus (donor) to the other (recipient) via placental vascular communications
- Arterio-arterial
- Veno-venous
- Arterio-venous
- Deep, unidirectional flow
Pathophysiologic evidence is indirect

Twin Twin Transfusion Syndrome
“the common denominator”

Twin Twin Transfusion Syndrome Diagnosis

- Single placenta
- Discordant amniotic fluid volumes
  - Polyhydramnios (MVP > 8cm) [< 20 wks; > 10 cm ≥ 20 wks]
  - Oligohydramnios (MVP > 2cm)
- Concordant for sex

Prediction of Twin Twin Transfusion

Nuchal Translucency
Folding Intertwin Membrane
Arterio-arterial anastomoses
Velamentous Cord Insertion

Timely Diagnosis of TTTS by Biweekly 2nd Trimester Sonography and Patient Education

Monochorionic twins TTTS (17%)
Ultrasound Screening*
  - Nuchal translucency
  - Membrane folding
  - EFW
Deepest vertical pocket 50%
Doppler: UA, UV, DV
Patient Education
  - Increase Abdominal Girth
  - Uterine Contractions

Recommendations:
- Biweekly ultrasounds >16 weeks for all MC Twins
- Detailed patient education

Sueters M et al Ultrasound Obstet Gynecol 2006;28:659
### Twin-Twin Transfusion Syndrome Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oligohydramnios (&lt;2cm) with Polyhydramnios (&gt;8cm)</td>
</tr>
<tr>
<td>II</td>
<td>Discordant fluid volumes No bladder in the donor twin</td>
</tr>
<tr>
<td>III</td>
<td>Doppler flow: absent or reversed in umbilical artery or ductus venosus, pulsatile flow in umbilical vein</td>
</tr>
<tr>
<td>IV</td>
<td>Hydrops in one or both fetuses</td>
</tr>
<tr>
<td>V</td>
<td>One or both fetuses have died</td>
</tr>
</tbody>
</table>

Quintero R et al. J. Perinatol 1999;19:55

### Treatment for TTTS

- Serial Amnioreduction
- Amnioreduction w/ Septostomy
- Selective reduction of umbilical cord occlusion
- **Fetoscopic laser ablation of placental anastomoses**
  - Sequential laser
  - Gestational age limits [16-26 wks]
  - Contraindications
    - Short Cervix – center specific
    - PROM
    - Chorioamnion Separation
    - Hemorrhage/Hematoma

### Intervention for the treatment of TTTS Laser vs. Amnioreduction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Laser Relative Risk (95% CI)</th>
<th>Amnioreduction Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual Death</td>
<td>0.33 (0.16-0.67)</td>
<td>1.00</td>
</tr>
<tr>
<td>Overall Death</td>
<td>0.71 (0.55-0.92)</td>
<td>1.00</td>
</tr>
<tr>
<td>Less Perinatal Death</td>
<td>0.59 (0.40-0.87)</td>
<td>1.00</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>0.29 (0.14-0.61)</td>
<td>1.00</td>
</tr>
<tr>
<td>Neurologically intact at 6 months</td>
<td>1.66 (1.17-2.35)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### Laser Learning Curve

Reports 1995-2017


The Fetal Center
30-day Survival Rate ~ Procedure GA 
(09/11-08/17)

<table>
<thead>
<tr>
<th>Gest Age Procedure</th>
<th>TOTAL</th>
<th>Twins</th>
<th>Singleton</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-18 weeks</td>
<td>89</td>
<td>65%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>19-21 weeks</td>
<td>132</td>
<td>77%</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>22-24 weeks</td>
<td>75</td>
<td>75%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>25-27 weeks</td>
<td>27</td>
<td>70%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>323</td>
<td>72%</td>
<td>15%</td>
<td>13%</td>
</tr>
</tbody>
</table>

The Fetal Center
30-day Survival Rate ~ TTTS Stage 
(09/11-08/17)

<table>
<thead>
<tr>
<th>TTTS Stage</th>
<th>TOTAL</th>
<th>Twins</th>
<th>Singleton</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>43</td>
<td>84%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>II</td>
<td>96</td>
<td>76%</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>III</td>
<td>166</td>
<td>68%</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>67%</td>
<td>26%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Preoperative predictors of IUFD after laser photoacoagulation for TTTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Variable Description</th>
<th>IUFD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zikuining L 1999</td>
<td>Aminoreduction</td>
<td>Both</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Inter/twin discordant AC</td>
<td>Donor</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>A/R a wave DV</td>
<td>Recip</td>
<td></td>
</tr>
<tr>
<td>Martinez J, 2003</td>
<td>AREDF UA</td>
<td>Donor</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>R A-wave DV</td>
<td>Donor</td>
<td>0.007</td>
</tr>
<tr>
<td>Skupski D 2010</td>
<td>EFV</td>
<td>Donor</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>R A-wave DV</td>
<td>Donor</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Hydrospr</td>
<td>Recip</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recip</td>
<td>0.04</td>
</tr>
<tr>
<td>Eixarch, E 2013</td>
<td>MCA PSV &gt; 1.5 MOM</td>
<td>Donor</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>REDF UA</td>
<td>Donor</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Fetal EFW &gt; 30%</td>
<td>Donor</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>GA Procedure &lt; 22 wks</td>
<td>Donor</td>
<td>0.046</td>
</tr>
</tbody>
</table>

The Fetal Center
Mean Gestational Age Delivery 
TTTS Post Laser

32 weeks

Etiology for Delivery TTTS Post Laser 
(n = 203*)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated</td>
<td>1.70 (1.11-2.91)</td>
<td>0.015</td>
</tr>
<tr>
<td>iPPROM</td>
<td>2.42 (1.93-3.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cervical Length</td>
<td>0.98 (0.98-0.007)</td>
<td>0.004</td>
</tr>
<tr>
<td>Amnioninfusion</td>
<td>1.50 (1.20-1.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cannula diameter 12 Fr</td>
<td>1.33 (1.01-1.74)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Risk Factors Associated with Preterm Delivery after Laser ablation in TTTS 
(29-33wks)

The Fetal Center

30-day Survival Rate ~ Cervical Length
(09/11-08/17)

<table>
<thead>
<tr>
<th>Cervical Length</th>
<th>TOTAL</th>
<th>Twins</th>
<th>Singleton</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 cm</td>
<td>306</td>
<td>874%</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>&lt; 1.5 cm</td>
<td>16</td>
<td>44%</td>
<td>12%</td>
<td>44%</td>
</tr>
</tbody>
</table>

TTTS

Neurologic Outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Percent follow-up</th>
<th>Age @ follow-up</th>
<th>Major abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salomon, 2009</td>
<td>73</td>
<td>96%</td>
<td>60 mo</td>
<td>16%</td>
</tr>
<tr>
<td>Lopriore, 2017</td>
<td>278</td>
<td>94%</td>
<td>48 mo</td>
<td>CP ~ 5% NDI ~ 6%</td>
</tr>
<tr>
<td>Rossi, 2011</td>
<td>695</td>
<td>97%</td>
<td>Birth</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>1255</td>
<td>97%</td>
<td>6-48 mo</td>
<td>11%</td>
</tr>
</tbody>
</table>

Cerebral lesions ~ Antenatal origin: 52-67%

Twin Anemia-Polycythemia Sequence (TAPS)

- Larger intertwin hemoglobin difference w/o signs of TOPS
- Intertwin blood transfusion w/o hormonal imbalance
- Post laser: ex-recipient anemic w/ ex-donor polycythemic
- Spontaneous reported as early as 16 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Post-laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robyr, 2006</td>
<td>101</td>
<td>13%</td>
</tr>
<tr>
<td>Habli, 2009</td>
<td>152</td>
<td>2%</td>
</tr>
<tr>
<td>Slagehekke, 2010</td>
<td>276</td>
<td>8%</td>
</tr>
<tr>
<td>Lewi et al, 2009</td>
<td>202</td>
<td>5%</td>
</tr>
<tr>
<td>Lopriore, 2010</td>
<td>113</td>
<td>5%</td>
</tr>
</tbody>
</table>

TAPS: Classification

<table>
<thead>
<tr>
<th>Antenatal Finding as Doppler Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 MAC-PSV: Donor &gt; 1.5 &amp; Recipient &lt; 1.0 MOM</td>
</tr>
<tr>
<td>Stage 2 MCA-PSV: Donor &gt; 1.7 &amp; Recipient &lt; 0.8 MOM</td>
</tr>
<tr>
<td>Stage 3 Stage 1 or 2, with Cardiac compromise in donor</td>
</tr>
<tr>
<td>Stage 4 Donor hydrops</td>
</tr>
<tr>
<td>Stage 5 IUFD of one or both</td>
</tr>
</tbody>
</table>

MCA PSV should be included in screening all MC Multifetal pregnancies

Fetoscopic laser coagulation of the vascular equator versus selective coagulation for TTTS
An open-label RCT

Placenta that was treated using the standard technique
Placenta that was treated using the Solomon technique
Solomon Trial RCT
Laser Vascular Equator vs. Selective Coagulation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Solomon Group (234 fetuses)</th>
<th>Standard Laser (270 fetuses)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>34%</td>
<td>49%</td>
<td>0.54 (0.35-0.82)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>74%</td>
<td>73%</td>
<td>NS</td>
</tr>
<tr>
<td>ALOS</td>
<td>85%</td>
<td>87%</td>
<td>NS</td>
</tr>
<tr>
<td>Dual Survival</td>
<td>64%</td>
<td>60%</td>
<td>NS</td>
</tr>
<tr>
<td>TAPS</td>
<td>3%</td>
<td>16%</td>
<td>0.16 (0.05-0.49)</td>
</tr>
<tr>
<td>Recurrent TTTS</td>
<td>1%</td>
<td>7%</td>
<td>0.21 (0.04-0.98)</td>
</tr>
<tr>
<td>Neuro Morbidity</td>
<td>8%</td>
<td>13%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Slaghekke F et al Lancet 2014

Vascular Occlusion Injuries in TTTS
- 95% recipient
- 85% lower limb
- 71% right sided
- Intestinal atresia
- Mechanism:
  - Polycythemia
  - Hyperviscosity
  - Hypertension
  - Vasocostriction

Schrey S et al AJOG 2012

Algorithm for Differential Diagnosis in MC Twins

AF MVP >8 cm (>10 cm ) / < 2 cm  Yes  TTTS
Bladder very large / very small-non visible

EFW < 10th % tile (+/- >20-25%)  Yes  sIUGR

MCA PSV > 1.5 & 0.8 MOM  Yes  TAPS

Not:
- AF Discordance
- EFW Discordance

Gratacos E et al Fetal Diagn Ther 2012;32:145-155

Conclusion Treatment & Management of TTTS
- Expectant Management ~ PMMR 80-90%
- Placental laser photocoagulation
  - Only proven therapy to reverse cardiovascular programming
  - SOC: Stage II-IV at 16-26 weeks
    - Role <16 and >26 weeks preliminary reports promise
    - Stage 1 ?
- Not a panacea
  - Survival: Dual intact ~ 60-70% with ALOS ~80-90%
  - Donors 60% vs. Recipient 70% [discordance EFW]
  - Developmental impairment 11-16% (cerebral palsy 5%)

Diaphragmatic Hernia
**Diaphragm Hernia**

- 1-4/10,000 live births
- Neonate
  - Defect requiring surgical repair
  - Pulmonary hypoplasia
  - Respiratory insufficiency
  - Pulmonary hypertension
- 2nd tri diagnosis SR > 60%
- Tertiary referral
  - Advanced imaging
  - Genetic testing
  - Multidisciplinary management

---

**CDH ~ Long Term Morbidity**

- Scoliosis
- Pulmonary hypoplasia
- Respiratory insufficiency
- Pulmonary hypertension
- Multiple operations
- GERD
- Infection
- Chronic lung disease

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**CDH: Open Fetal Repair**

Anatomical repair of the hernia through open hysterotomy proved feasible, but it did not decrease mortality and was abandoned.

---

**Fetal Lamb Tracheal Ligation & CDH Reversal of Structural & Physiologic Effects**

**Purpose:** Can lung growth be accelerated in the setting of experimental pulmonary hypoplasia.

**Method:** 95 day gestation fetal sheep were divided into four groups: nephrectomy (NP), NP/TL, TL alone, and sham-operated control animals.

**Results:** NP smaller lungs than control, NP/TL larger lungs when compared with NP and the controls.

**Concluded:**
1. TL accelerated lung growth beyond normal limits even in the absence of fetal kidneys;
2. Lung growth is achieved in part by cell proliferation;
3. Lung architecture remains relatively normal,
4. Pulmonary hypoplasia associated with CDH may be preventable by tracheal occlusion.


---

**Fetal Tracheal Clip Application Laparotomy**

“Open” – Hysterotomy

“Fetoscopic” – 2-Port

---

**Sonographic Predictors of Survival in Fetal Diaphragmatic Hernia**

<table>
<thead>
<tr>
<th>N</th>
<th>Survival</th>
<th>LHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0%</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>28</td>
<td>57%</td>
<td>&gt; 0.6 - 1.35</td>
</tr>
<tr>
<td>5</td>
<td>100%</td>
<td>&gt; 1.35</td>
</tr>
</tbody>
</table>

- Postnatal survival directly related to LHR
- Large difference in reported results
- Measured at different gestational ages
- Method of measuring LHR


**Metkus AP J Pediatr Surg 1996; 31:24**
Sonographic Predictors of Survival in Fetal Diaphragmatic Hernia

<table>
<thead>
<tr>
<th>N</th>
<th>Survival</th>
<th>LHR</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>0%</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>28</td>
<td>57%</td>
<td>&gt; 0.6 - &lt; 1.35</td>
</tr>
<tr>
<td>5</td>
<td>100%</td>
<td>&gt; 1.35</td>
</tr>
</tbody>
</table>

- Postnatal survival directly related to LHR
- Large difference in reported results
- Measured at different gestational ages
- Method of measuring LHR


Diaphragmatic Hernia NIH Randomized Trial

<table>
<thead>
<tr>
<th></th>
<th>Standard Treatment</th>
<th>Tracheal Occlusion</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>PROM</td>
<td>23%</td>
<td>100%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PTL</td>
<td>31%</td>
<td>73%</td>
<td>0.10</td>
</tr>
<tr>
<td>Abruption</td>
<td>8%</td>
<td>27%</td>
<td>0.30</td>
</tr>
<tr>
<td>GA_Del</td>
<td>37.0 + 1.5</td>
<td>30.8 + 2.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Survival 90 days</td>
<td>77%</td>
<td>73%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

LHR < 1.4 with liver herniation


Antenatal Left Sided Diaphragm Hernia Survival Rates LHR O/E and Liver Position

<table>
<thead>
<tr>
<th>o/e LHR</th>
<th>Liver</th>
<th>N</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>Up</td>
<td>39</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Down</td>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>25-34%</td>
<td>Up</td>
<td>65</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Down</td>
<td>44</td>
<td>66%</td>
</tr>
<tr>
<td>35-44%</td>
<td>Up</td>
<td>27</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>Down</td>
<td>47</td>
<td>77%</td>
</tr>
<tr>
<td>&gt;45%</td>
<td>Up</td>
<td>16</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Down</td>
<td>67</td>
<td>87%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Up</td>
<td>161</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Down</td>
<td>168</td>
<td>75%</td>
</tr>
</tbody>
</table>

UCLA

Modified from Deprest et al. 2014

European Consortium Fetoscopic Tracheal Occlusion (FETO)

EUROFETUS Modification FETO Instruments

Europetus NAFTNet UCSF

BALT Goldballoon & Catheter
Designed especially for the embolisation of arterio-venous malformations and blood vessel occlusion.


Isolated Left Side DH ~ 29 4/7 weeks

Severe Left Sided CDH treated with FETO
Predictor of Postnatal Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>144</td>
<td>54%</td>
</tr>
<tr>
<td>o/e LHR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td>15</td>
<td>20%</td>
</tr>
<tr>
<td>16-20</td>
<td>53</td>
<td>59%</td>
</tr>
<tr>
<td>21-25</td>
<td>56</td>
<td>54%</td>
</tr>
<tr>
<td>26-30</td>
<td>20</td>
<td>70%</td>
</tr>
</tbody>
</table>

Doubling Survival Rate

FETO in Severe CDH
Associated with a substantial improvement in survival.

Cochrane Database of Systematic Review

Conclusion

• The current evidence is too limited by small numbers of pregnancies and variable methodological quality of the trials to date to recommend intervention (FETO) in pregnancy for women and their unborn babies with CDH.

<table>
<thead>
<tr>
<th>RCT Study</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison, MR, NEJM 2003</td>
<td>24</td>
</tr>
<tr>
<td>Ruano R, UOG, 2012</td>
<td>41</td>
</tr>
</tbody>
</table>

TOTAL Trial ~ Two randomized trials

TOTAL Trial Hypothesis

Prenatal intervention, fetoscopic tracheal occlusion will have a 50% increase of the expected survival rate in fetuses with isolated CDH and severe pulmonary hypoplasia.
**TOTAL Trial**

**Inclusion**
- Singleton fetus
- Isolated left-sided CDH
- Normal Karyotype
- Severe Group
  - O/E LHR <25 %
  - Irrespective of liver position
- Moderate Group
  - O/E LHR 25-34.9%, liver up or down
  - O/E LHR 35-44% liver up

**Exclusion**
- Maternal contraindication to fetal intervention
- Technical or maternal limitation to fetoscopy
- He preterm labour
- Cervix length <15 mm
- Refusal to remain in proximity to FETO center during time period of airway occlusion

**Exclusion**
- Maternal contraindication to fetal intervention
- Technical or maternal limitation to fetoscopy
- He preterm labour
- Cervix length <15 mm
- Refusal to remain in proximity to FETO center during time period of airway occlusion

**Postnatal Treatment**
Expectant management during pregnancy postnatal repair.
Standardized neonatal intensive care

---

**FETO Participating Center Requirements**

- FETO Center
  - Fetoscopic Program ~ 36/year
  - Postnatal CDH Program ~ 7/year
- Local PI
  - Proficiency
    - Participating in 15 cases
    - 5 cases performed locally – Feasibility Studies

---

**BALT Occlusive Device**

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**TOTAL Team Training Simulation and Animal**

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**FETO Simulation Model**

---

**Pilot Trial of FETO in Left CDH Feasibility Study**

**Study Type:** Interventional

**Study Design:**
- Endpoint: Safety/Efficacy Study
- Interventional Model: Single group assignment
- Masking: Open Label
- Primary Purpose: Treatment

**Primary Outcomes**
- Successful placement & removal of BALT Goldbal2 balloon
- Gestational age of delivery

**Secondary Outcomes**
- Lung Volume & LHR after FETO
- Survival 6 months

Ultimate goal to enter TOTAL Trial
**TOTAL TRIAL ~LIMITATIONS**

- Backdoors ~ Balloons placed outside the trial
- European ~ Lack of Equipoise
  - **Pessimistic**: survival rate with expectant management
  - **Optimistic**: suggest outcomes better with FETO

**TOTAL Trial & CDH**

- CDH is a rare disorder
- Concentrating treatment in high volume regional centers with expertise ~ common sense
- Experience is related to efficacy
  - Improved perioperative assessment
  - Shorten "learning curve"
    - Shorten Operative times
    - Reduced PPROM
- Overall Maternal Fetal Outcomes

**Cochrane Database of Systematic Review**

**Conclusion**

- Further high-quality trials are need in this area
- FETO should only be offered within the framework of ongoing clinical trial.

**Time Line for Future Events in Fetal Intervention**

**Fetal surgery for spina bifida:**
A paradigm shift for modern fetal centers

KuoJen Tsao, MD
Professor of Pediatric Surgery
Professor of Obstetrics and Gynecology
University of Texas McGovern Medical School at Houston
Co-Director, The Fetal Center
Fetal Surgery

Application of established surgical techniques to the unborn baby
• During gestation
  • At end of gestation

To improve perinatal outcome for fetuses with malformations.
• To prevent fetal death
  • Lung masses
  • Sacrococcygeal teratoma
  • Twin twin transfusion syndrome

• To prevent neonatal death or reduce long-term morbidity
  • Giant neck masses
  • Congenital diaphragmatic hernia
  • Congenital heart lesions
  • Spina bifida*

Fetal Surgery: Balancing Risks

• Natural hx of fetal anomaly
• Fetal surgical risks

Risks to Mother

Spina Bifida

Meningomyelocele with Arnold Chiari Malformation
Spina bifida

4,000 babies are born per year in the United States

Hospital cost after birth:
- Median $29,000 (range: $100 - $1,300,000)

Cost of caring for a spina bifida:
- $636,000 per person for life
- $200 million per year

Long-term morbidity associated with spina bifida
- Unable to independently walk
- Bowel and bladder control problems
- Hydrocephalus - shunt placement
- Mental retardation
- Sexual dysfunction

What is spina bifida?

Spina bifida is a congenital abnormality in which the normal fusion of the spinal cord fails to occur.

Rationale for In-utero Spina Bifida Repair

#1. Prevent leakage of CSF
- Reverse Chiari II malformation

#2. Prevent damage to spinal cord
- Preserve spinal cord function
At 36 days there is almost complete fusion of the spinal cord.

By 42 days there should be complete fusion of the spinal cord.

If the tissue fails to close near the head, a condition known as anencephaly can occur.

There are four types of spina bifida.
A Meningocele is defined as an open neural tube defect that contains only fluid.

Myelomeningocele is defined as an open neural tube defect that contains both fluid and nerve tissue.

The third type is a "Covered neural tube defect" that is covered by skin without any outpouching.

Spina bifida defects are open with any covering or outpouching, known as non-covered neural tube defects.

As you can see, there is an opening in the spinal cord that allows an outpouching of tissue.
In a normal brain, the brain tissue contains and is surrounded by cerebral spinal fluid or CSF.

When the CSF leaks and causes hydrocephalus, a Chiari II malformation can occur.
Management of Myelomeningocele Study (MOMS Trial)

- Fetal Surgery vs Routine Care
- NIH funded
- 3 Centers
  - University of California, San Francisco
  - Children's Hospital of Pennsylvania
  - Vanderbilt Medical Center
- 8 years
- $22.5 million

Goal

To compare the safety and efficacy of in utero repair of myelomeningocele with that of the standard postnatal repair

Study Design

- Unmasked randomized trial
- Fetal versus postnatal closure of myelomeningocele
- Sample size 200
- Central preliminary screening and assignment to MOMS center
- Central randomization
- Outcome evaluation by blinded independent investigators

Inclusion Criteria

- Myelomeningocele defect starting between T1-S1
- Evidence of hindbrain herniation
- Singleton pregnancy 19º to 25º weeks
- Normal karyotype
- Resident of USA
- At least 18 years old

Exclusion Criteria

- Additional anomalies
- HIV or Hepatitis B positive
- If known to be Hepatitis C positive
- Increased risk for preterm delivery
  - short cervix (< 2.5 cm)
  - cerclage
  - uterine anomaly
  - placenta previa
  - prior spontaneous preterm delivery
- Unable to comply with travel, need for support
- Psychosocial issues preventing compliance
- Fetal kyphosis ≥ 30 degrees
- Maternal IDDM
- Isoimmunization
- Body mass index ≥ 35
- Other contraindications to elective surgery

MOMS Center patient referral distribution
Evaluation at MOMS Center

- 2-day comprehensive evaluation
- Medical Evaluation
  - History and physical
  - Ultrasound
  - Fetal MRI
  - Fetal echocardiogram
  - Beck Depression Inventory
- Consultation with team
  - Fetal surgeon
  - Perinatologist
  - Neurosurgeon
  - Neonatologist
  - Anesthesiologist
  - Social worker
  - Ethicist
  - Nurse coordinator

If Randomized to Prenatal Surgery

- Surgery 1-3 days after randomization
- Before 26 weeks
- Standardized surgical technique
- Postoperative tocolytic therapy
- Patient in local accommodation until delivery
- Two weeks bedrest post-op
- Weekly visits to MOMS center
- Delivery by C-section at 37 weeks

If Randomized to Postnatal Surgery

- Patient returned home for prenatal care
- Monthly ultrasounds by local physician
- Return to MOMS center at 37 weeks for fetal lung maturity testing
- Cesarean delivery if fetal lung maturity
- Neonatal repair by MOMS neurosurgical team

MOMs Follow-up Exams

- Patient, support person and infant travel to MOMS center
- 12 and 30 months
- Independent follow-up teams
  - Pediatrician
  - Psychologist
- Appointed by the Data Coordinating Center
- No affiliation with MOMS Center
- Blinded to treatment assignment

MOMS Trial Accounting

- 1087 screened through GWU
- 530 excluded
- 258 declined evaluation
- 299 evaluated at MOMS centers
- 75 excluded
- 41 declined
- 183 randomized
- 92 open fetal closure
  - 80 included in 12 month
  - 70 included in 30 month
- 91 postnatal repair
  - 78 included in 12 month
  - 64 included in 30 month

Primary Outcome at 12 months

- Death
- Need for ventricular decompressive shunting
  - Need determined by independent neurosurgeons with defined by objective criteria
  - Blinded to randomization
Infant Outcomes at 12 Months

<table>
<thead>
<tr>
<th></th>
<th>Prenatal Surgery (n=78)</th>
<th>Postnatal Surgery (n=80)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome (%)</td>
<td>68 98</td>
<td>0.70(0.58-0.84)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt criteria met</td>
<td>65 92</td>
<td>0.48(0.36-0.64)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Any hindbrain herniation</td>
<td>64 96</td>
<td>0.67(0.56-0.81)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Placement of shunt (%)</td>
<td>40 82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>40 29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>19 45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>6 22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Outcome at 30 months
- BSID - mental development index (MDI)
- Difference between the motor and lesion level
  - Lesion level determined radiographically
  - Functional level examination
    - Motosensory
    - Somatosensory

Infant Outcomes at 30 Months

<table>
<thead>
<tr>
<th></th>
<th>Prenatal Sx N=64</th>
<th>Postnatal Sx N=70</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome score</td>
<td>148.6±57.6</td>
<td>122.6±57.2</td>
<td>0.007</td>
</tr>
<tr>
<td>BMDI - MDI</td>
<td>89.7±14.0</td>
<td>87.3±18.4</td>
<td>0.53</td>
</tr>
<tr>
<td>Difference between</td>
<td>0.58±1.94</td>
<td>-0.69±1.99</td>
<td>0.001</td>
</tr>
<tr>
<td>anatomic level &amp; functional level</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difference (%)
- ≥ 2 levels better: 32 12 0.005
- 1 level better: 11 9
- no difference: 23 25
- 1 level worse: 21 25
- ≥ 2 levels worse: 13 28 0.03

Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Prenatal Surgery (N=64)</th>
<th>Postnatal Surgery (N=70)</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not walking (%)</td>
<td>29 43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking with assistance (%)</td>
<td>29 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking independently (%)</td>
<td>42 21</td>
<td>2.01 (1.16-3.48)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Pregnancy Complications

<table>
<thead>
<tr>
<th></th>
<th>Prenatal Surgery (N=78)</th>
<th>Postnatal Surgery (N=80)</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorionamniotic Separation (%)</td>
<td>26 0</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Edema (%)</td>
<td>6 0</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Oligohydramnios (%)</td>
<td>23 6</td>
<td>5.47(1.66-18.96)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Abruption (%)</td>
<td>6 0</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>SROM (%)</td>
<td>46 8</td>
<td>6.15(2.75-13.78)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Spontaneous labour (%)</td>
<td>38 14</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Transfusion at delivery (%)</td>
<td>9 1</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Scar dehiscence at delivery (%)</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pregnancy outcomes

Maternal outcomes

VP shunt outcomes

- During an 8 year period over 1,000 pregnant mothers were initially screened for the MOMs Trial.

There are two patients that are undergoing an operation: the fetus with spina bifida and the pregnant mother.
Recommendation
Women who meet the criteria outlined in MCMs Trial should be made aware of the study findings and counseled regarding the option of maternal fetal surgery for MMC including risks/benefits and implications to future pregnancies.
**Clinical Opinion**

Position statement on fetal myelomeningocele repair

- American Academy of Pediatrics
- American College of Obstetricians and Gynecologists
- American Institute of Ultrasound in Medicine
- American Pediatric Surgical Association
- American Society of Anesthesiologists
- American Society of Pediatric Neurosurgeons
- International Fetal Medicine and Surgery Society
- American Association of Neurological Surgeons/Congress of Neurological Surgeons
- Society on Pediatric Neurological Surgery
- North American Fetal Therapy Network
- Society for Maternal-Fetal Medicine
- Society of Pediatric Anesthesia
- Spina Bifida Association

**Controversies**

**Extended criteria**

**BMI Greater than 35**
Pre-Pregnancy BMI may be greater than 35 kg/m² but must be less than or equal to 40 kg/m².

**Structural Abnormality**
Must be a minor abnormality that will not increase the risk of prematurity. Some examples include cleft lip & palate, a minor ventricular septal defect, pyelectasis, etc. A normal chromosomal microarray will also be required. This test can be done from the amniotic fluid taken during your amniocentesis.

**Diabetes**
Diabetic patients will require good glycemic control, for example a normal hemoglobin A1C at the start of pregnancy and compliance with insulin injections or pump therapy.

**A Previous Preterm Birth**
If you have a history of a previous spontaneous singleton delivery (born before 37 weeks) followed by a full term delivery.

**Maternal-Fetal Rh Alloimmunization**
Must meet one of the following: 1. A low level of anti-red blood cell antibody that is not associated with fetal disease, specifically, anti-E < 1:4 or anti-N 2. Alloimmunization cases with a negative fetal red cell antigen status determined by amniocentesis.

**Minimally invasive fetoscopic repair**

**Ventricular size**

**Fetal Therapy: The Future**
Stem Cell Therapy

- Brain injury due to congenital heart defects
- Stem cell derived cardiac patches
- Genetic disorders

Fetal Tissue Engineering

Future goals to repair

- Water tight seal of the defect to prevent hind brain herniation
- Reduce scarring and spinal cord tethering
- Repair at an earlier gestational age
- Minimally invasive spina bifida repair

Human case: HUC for in-utero repair of Spina Bifida at 23 weeks

Skin defect after delivery (37 weeks)
Reverse of hindbrain herniation

Spinal Cord and Clinical Outcomes

- Normal head size
- Normal both leg movements
- Normal bladder and bowel control

Minimal spinal cord scarring

Faith at 1 year

Questions/comments