Open Fetal Surgery for Myelomeningocele Closure

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Professor, Department of Obstetrics, Gynecology and Reproductive Services
Objectives

By the end of this talk you should be able to:

• Understand how the concept of ‘benefit’ is evolving in determining which anomalies can be ‘corrected’ by open maternal-fetal surgery.

• Be able to counsel patients about the risks and benefits of open maternal-fetal surgery for fetuses with myelomeningocele

• Outline the evaluation process to determine who is a candidate for open maternal-fetal surgery.
It’s Controversial!

1. How did we get here?
2. What can we do?
3. Does open fetal surgery alter the natural history of MMC?
4. Are benefits clearly demonstrable?
Myelomeningocele
Myelomeningocele

Long-term Consequences: The Burden of Disease

✓ Hydrocephalus
  • Hindbrain herniation
  • VP shunts
  • variable cognitive impairment

✓ Nerve damage
  • paralysis of legs & feet
  • bowel & bladder incontinence

✓ Orthopedic deformities
  • spine
  • pelvis
  • lower limbs

✓ Social and emotional challenges
## Texas Birth Defect Registry – Spina Bifida
### Pregnancy Outcome - Years 2000 - 2009

<table>
<thead>
<tr>
<th></th>
<th>Live Birth</th>
<th>Spontaneous Fetal Death</th>
<th>Induced Pregnancy Termination</th>
<th>Unspecified Fetal Death / Termination</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1244</td>
<td>61</td>
<td>89</td>
<td>0</td>
<td>1394</td>
</tr>
<tr>
<td>%</td>
<td>89.24</td>
<td>4.38</td>
<td>6.38</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Texas Department of State of Health Services; Birth Defect Registry for Years 2000 - 2009
Texas Birth Defect Registry – Spina Bifida
Volume by Year

Cases

Prevalence

Source: Texas Department of State of Health Services; Birth Defect Registry for Years 2000 - 2009
Texas Birth Defect Registry – Spina Bifida Demographics

Hispanic: 4.17 per 10,000
Non-Hispanic Black or African-American: 2.64 per 10,000
Non-Hispanic White: 3.22 per 10,000

The 2009 estimate of medical costs for the first year of life for a child with spina bifida was $52,415.
The lifetime medical cost\(^1\) for a person with spina bifida was estimated to be $460,923 in 2009.
The lifetime nonmedical cost\(^2\) for a child with spina bifida, which includes education and developmental services such as early intervention services and counseling, was estimated to be $56,511 in 2009.

Source: CDC Spina Bifida Facts
http://www.cdc.gov/ncbddd/spinabifida/facts.html
What’s the Theory?
2 Hit Hypothesis

First Hit: Failure of neurulation
(but normal neural development?)

Secondary damage acquired in utero

Fetal Surgery?
Fetal Sheep Surgery
In utero coverage of MMC

Rescues neurologic function at birth
Successful fetal surgery for spina bifida

N Scott Adzick, Leslie N Sutton, Timothy M Crombleholme, Alan W Flake

Spina bifida occurs in one of 2000 livebirths and leads to lifelong and devastating physical disabilities including paraplegia, hydrocephalus, incontinence, sexual dysfunction, skeletal deformations, and mental impairment. Compelling experimental evidence shows that the neurological deficit associated with open spina bifida is not entirely caused by the primary defect of neurulation, but rather is due to chronic mechanical injury and amniotic fluid-induced chemical trauma that progressively damages the exposed unprotected fetal neural tissue during gestation. Timely in-utero repair of spina bifida in fetal sheep stops the ongoing spinal cord destruction and “rescues” neurological function by the time of birth. In late-gestation human fetuses and in neonates with spina bifida, the neural tissue elements show severe traumatic and degenerative alterations, or there is almost complete loss of neural tissue. Sonographic reports of human fetuses with very large spina bifida lesions and normal leg movements early in gestation imply that motor function is present initially and lost only later in gestation. We report the first successful in-utero surgical repair of open spina bifida in an early-gestation fetus.

A 27-year-old woman was referred for assessment of a
A. Patient position

Laparotomy incision
B  Stapled hysterotomy

Myelomeningocele

Incision along arachnoid and skin junction

Neural placode

Irrigation tube
C Myelomeningocele repair

- Edge of myometrium and chorioamniotic membranes
- Neural placode
- Closure of dura mater
- Myofascial flap
- Skin edge
Human Myelomeningocele Closure

• Retrospective review of first 50 cases

• Selection criteria:
  ✓ gestational age < 26 wks
  ✓ normal karyotype
  ✓ absence of other anomalies
  ✓ ventriculomegaly < 17 mm
  ✓ type II Arnold-Chiari malformation
  ✓ intact neurologic function in the lower extremities
Demographics:

- mean maternal age: 30.4 yrs. (18-40)
- primigravida = 13, multiparous = 37
- defect level by MRI: thoracic = 4 (highest T8)
  lumbar = 39
  sacral = 7 (lowest S1)
- Chiari II: grade II = 7, grade III = 43
- Mean ventriculomegaly = 11.2 mm (5.6 – 16.1)
- Mean GA at surgery = 23 wks 0 day (20w0d - 25w4d)
- Mean post-operative hospital stay = 4.5 days

Human Myelomeningocele Closure

Post operative findings:

- **mean GA at delivery = 34w4d**
- mean birthweight = 2354 gm
- median APGAR = 8/9
- hysterotomy dehiscence/rupture = 0/40
- fetal deaths = 3/50 (6.0%)
- mean lateral ventricular diameter at birth = 16.2 mm
- mean ▽ in lateral ventricular diameter during pregnancy= 5.5 mm
- **reversal of hindbrain herniation at 6 wks. post-op MRI = 47/48**

Human Myelomeningocele Closure
Obstetrical Complications

- Postop oligohydramnios: 3/50 (6%)
- Chorioamniotic Separation: 14/50 (28%)
  2/50 (4%) admitted for bedrest & monitoring
- Preterm labor requiring tocolysis: 3/50 (6%)
- Delivery before elective C/S date @ 36 wks 22/50 (44%)
- Mean GA = 32 wks 2d
- No uterine dehiscence at time of delivery
- Maternal transfusion: 2/50 (4%)
Human Myelomeningocele Closure

Ventriculoperitoneal Shunt Placement = 20/47  (42.6%)  

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Expected*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>Lumbar</td>
<td>44%</td>
<td>88%</td>
</tr>
<tr>
<td>Sacral (S1)</td>
<td>20%</td>
<td>68%**</td>
</tr>
</tbody>
</table>

* rate based on skeletal lesion level in 297 patients followed from 1983-2000 in Spina Bifida Clinic at CHOP  
** observed rate for all sacral (S1-S4) lesion levels
Human Myelomeningocele Closure

Neurofunctional Difference Analysis

Expected

+ 2

Observed

- 2

Expected

UTHealth
The University of Texas
Health Science Center at Houston
Medical School

Texas Fetal Center

Children's Memorial Hermann Hospital
Human Myelomeningocele Closure

Neurofunctional Difference Analysis

<table>
<thead>
<tr>
<th>Better</th>
<th>Same</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>+2</td>
<td>+1</td>
<td>-1</td>
</tr>
<tr>
<td>57.4%</td>
<td>24.1%</td>
<td>18.5%</td>
</tr>
<tr>
<td>0%</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

fMMC  
pMMC
Human Myelomeningocele Closure

Lower extremity neuromotor function

- Mean age at follow-up 39.7±15.5 months
- Fetal MMC repair compared to cohort of postnatal MMC repair

<table>
<thead>
<tr>
<th></th>
<th>Walking</th>
<th>Braces</th>
<th>Walker</th>
<th>Wheelchair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal MMC n=40</td>
<td>21</td>
<td>8</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Postnatal MMC n=17</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
Human Myelomeningocele Repair

- majority of children scored in the average to high average range in cognitive testing
- show higher than predicted academic achievement particularly in math and reading
- improvement in scores was independent of shunt status by 5 years of age
- better than expected outcomes even extended into areas of visual-motor and spacial cognitive integration
MOMS
Management of Myelomeningocele Study

NEJM 364;993-1004:2011
Goal

To compare the safety and efficacy of in utero repair of open neural tube defects 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 $19^0$ to $25^6$ 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, cerclage, uterine anomaly, 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
Referral Map for MOMs Patients

[Map showing referral areas with major medical centers indicated]

- UCSF
- CHOP
- Vanderbilt

[Legend for map areas]
Evaluation at MOMS Center

- 2-day comprehensive evaluation
- Medical Evaluation: History and physical, ultrasound, fetal MRI, fetal echocardiogram, Beck Depression Inventory
- Meets with all members of the team: Maternal-fetal surgeon, perinatologist, neonatologist, social worker, ethicist, nurse coordinator, neurosurgeon, anesthesiologist
- Extensive counseling. Choices outlined:
  - Termination of pregnancy
  - Near term C/S with postnatal MMC repair
  - MOMS Trial if a candidate
If Randomized to Prenatal Surgery

- Surgery 1-3 days after randomization and before 26 weeks
- Standardized surgical technique
- Postoperative tocolytic therapy
- Patient in local accommodation until delivery (Ronald McDonald House)
- 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 at 12 and 30 months
• Conducted by independent follow-up teams consisting of a pediatrician and a psychologist
• Appointed by the Data Coordinating Center, teams have no affiliation with MOMS or Maternal-Fetal Surgery Center
• Teams 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)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Prenatal Surgery N=78</th>
<th>Postnatal Surgery N=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender (%)</td>
<td>45</td>
<td>64</td>
</tr>
<tr>
<td>GA at randomization (wks)</td>
<td>23.6±1.4</td>
<td>23.9±1.3</td>
</tr>
<tr>
<td>Maternal Age (yrs)</td>
<td>29.3±5.3</td>
<td>28.8±4.9</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>Married or living with partner (%)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2±3.7</td>
<td>25.9±3.9</td>
</tr>
<tr>
<td>Nulliparity (%)</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>Lesion L3 or lower on US (%)</td>
<td>68</td>
<td>84</td>
</tr>
<tr>
<td>Talipes on US (%)</td>
<td>26</td>
<td>19</td>
</tr>
</tbody>
</table>
Primary Outcome Measure

• Death, or the need for ventricular decompressive shunting by one year of age as defined by objective criteria

• To reduce bias, records of all infants are reviewed by an independent committee of neurosurgeons, blinded to treatment assignment, to determine whether criteria for shunting have been met
Criteria for Shunt

1. Cerebrospinal fluid leakage from the MMC wound or
2. Bulging at the myelomeningocele wound or
3. Any 2 of the following:
   - Increase in the greatest occipital-frontal circumference at a rate of greater than one centimeter per week.
   - Fontanelle bulging and pulsating or bulging and hard
   - Increasing hydrocephalus on 2 consecutive u/s or CTs determined by increase in ratio of biventricular diameter to biparietal diameter measured at the foramen of Monro or
4. In infants less than 1 week old a fontanelle evaluated as bulging and hard, together with ventriculomegaly and any of apnea, bradycardia or lethargy - or
5. Development of marked syringomyelia by MRI
# 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</td>
<td>98</td>
<td>0.70(0.58-0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt criteria met</td>
<td>65</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placement of shunt (%)</td>
<td>40</td>
<td>82</td>
<td>0.48(0.36-0.640)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any hindbrain herniation (%)</td>
<td>64</td>
<td>96</td>
<td>0.67(0.56-0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>36</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>40</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>19</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>6</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Outcome Measure 2

- A composite outcome of two measures at 30 months corrected age:
  - BSID - mental development index (MDI)
  - Difference between the motor level and lesion level
    - Lesion level determined radiographically
    - Functional level by motosensory & somatosensory examination
## 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 anatomic level &amp; functional level</td>
<td>0.58±1.94</td>
<td>-0.69±1.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Difference (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2 levels better</td>
<td>32</td>
<td>12</td>
<td>0.005</td>
</tr>
<tr>
<td>1 level better</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>no difference</td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1 level worse</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>≥ 2 levels worse</td>
<td>13</td>
<td>28</td>
<td>0.03</td>
</tr>
</tbody>
</table>
## Infant Outcomes at 30 Months

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

<table>
<thead>
<tr>
<th>Complication</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>Chorioamniotic Separation (%)</td>
<td>26</td>
<td>0</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary Edema (%)</td>
<td>6</td>
<td>0</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Oligohydramnios (%)</td>
<td>21</td>
<td>4</td>
<td>5.47(1.66-18.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abruption (%)</td>
<td>6</td>
<td>0</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>SROM (%)</td>
<td>46</td>
<td>8</td>
<td>6.15(2.75-13.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spontaneous Labour (%)</td>
<td>38</td>
<td>14</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusion at delivery (%)</td>
<td>9</td>
<td>1</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Scar dehiscence at delivery (%)</td>
<td>10</td>
<td></td>
<td></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>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Gestational Age at Delivery (wks)</td>
<td>34.1±3.1</td>
<td>37.3±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;30 wks (%)</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>30-34 wks</td>
<td>33</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>35-36 wks</td>
<td>33</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>≥ 37 wks</td>
<td>21</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Mean Birth Weight (g)</td>
<td>2383±688</td>
<td>3039±469</td>
<td>&lt;0.001</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>Lost to follow-up</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</td>
<td>No shunt</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, 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>No shunt</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>G1P0</td>
<td>23 5/7</td>
<td>T12-S5</td>
<td>33</td>
<td>Shunted</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>G2P1</td>
<td>24 5/7</td>
<td>L4-S5</td>
<td>----</td>
<td>Admitted at 27 weeks ROM pregnancy ongoing</td>
</tr>
</tbody>
</table>
Open Fetal Surgery for MMC

- Fetal Surgery is not a cure
- Fetal Surgery is not a panacea
- Selection of appropriate candidates is important