Management of children with spina bifida in the age of fetal intervention

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Spina Bifida and Neural Tube Defects

**Epidemiology**

- One of the most common birth defects: 1-2 cases/1,000 births
  - Certain populations have a greater risk:
  - Highest incidence in Ireland and Wales
  - More common in girls
  - U.S.: 0.7/1,000 live births
  - Higher on the East Coast than on the West Coast
  - Higher in whites (1/1,000 births)
  - Lower in African-Americans (0.1-0.4/1,000 births)
Spina Bifida and Neural Tube Defects

• Epidemiology
  ○ Risk factors:
    - Race and ethnicity
    - Family history of neural tube defects
    - Folate deficiency
    - Medication/teratogenic effect: valproic acid
    - Maternal age
    - Diabetes
    - Obesity
    - Increased body temperature

Hol FA et al, Clinical Genetics, 2008
Management of children with spina bifida in the age of fetal intervention

- Embryology of spina bifida
  - Weeks 3-4 of gestation
  - 3 phases:
    - Neurulation
    - Canalization
    - Retrogressive differentiation
Spina Bifida and Neural Tube Defects

• Definitions and Classification
  o Open spina bifida (Aperta)
    ▲ Meningocele in 5%
    ▲ Myelomeningocele (cord and cauda equina exposed) in 95%
  o Closed spina bifida (Occulta)
    ▲ 50% have cutaneous stigmata
    ▲ Lipomyelomeningocele
    ▲ Filum terminale lipoma
    ▲ “Fatty” filum terminale
    ▲ Dermoid sinus and dermoid tumor
Spina Bifida and Neural Tube Defects

- Current management of spina bifida
  - Primary treatment
    - Perinatal care (protection of the neural tube, infections)
    - Closure of the defect
    - Management of hydrocephalus
    - Chiari II hindbrain herniation

Formal evaluation of spina bifida (overlaps with treatment)
- Physical examination: deformities, neuro exam; continence/tone
- Ultrasound
- MRI – brain
- MRI – spine
- Other: genetic testing, specialized imaging
Spina Bifida and Neural Tube Defects

- Definitive repair of the open neural tube defect
  - Posterior vertebral defect
  - Thecal sac
  - Cord extruded into the sac (placode)
    - Plate of embryonic epithelial cells: spinal cord
Definitive repair of the open neural tube defect

- Closure within 24 hours
- No evidence that immediate/urgent closure improves function
- *But*: early closure reduces risk of infection
  - Wound colonization after 36 hours

- Surgical technique: (neurosurgeon + plastic surgeon team)
  - Placode dissected off arachnoid
  - Allowed to drop into spinal canal
  - Dura dissected off skin and lumbodorsal fascia
  - Dura closed
  - Muscular fascia closed
  - Skin closed
Spina Bifida and Neural Tube Defects

- **Definitive repair of the open neural tube defect**
  - Surgical technique: Sharp microdissection of the placode
Spina Bifida and Neural Tube Defects

- **Definitive repair of the open neural tube defect**
  - Continued dissection toward the placode
  - Detethering
Spina Bifida and Neural Tube Defects

- **Definitive repair of the open neural tube defect**
  - Detethering of aberrant nerve roots
Spina Bifida and Neural Tube Defects

- Definitive repair of the open neural tube defect

Paraspinal muscle closure
Spina Bifida and Neural Tube Defects

- Definitive repair of the open neural tube defect
Spina Bifida and Neural Tube Defects

- Pathophysiology and associated disorders
- Hydrocephalus
  - 80-95% incidence in myelomeningocele
    - 100% of 35 thoracic lesions
    - 88% of 114 lumbar lesions
    - 68% of 40 sacral lesions
  - Significant in 20% at birth

Rintoul et al, Pediatrics 2002
Spina Bifida and Neural Tube Defects

- **Management of hydrocephalus**
  - Imaging: ventriculomegaly (Ventricular index > 0.33)
  - Pediatric characteristics:
    - Selective thinning of the occipital cranial vault and cortex:
      - Rigid nuclear masses (basal ganglia) in the frontal lobe
  - Monitor head circumference!
Spina Bifida and Neural Tube Defects

- Management of hydrocephalus
  - Serial head ultrasounds in the newborn:
Spina Bifida and Neural Tube Defects

- **Management of hydrocephalus**
  - Temporary drainage:
    - Lumbar puncture
    - External ventricular drainage, reservoir
  - **Shunt**
    - Weight >2.5 kg
    - No active infection
    - Medically stable
  - **Endoscopic third ventriculostomy**
Spina Bifida and Neural Tube Defects

- **Management of hydrocephalus**
  - **Types of shunts:**
    - Adjustable valves
Spina Bifida and Neural Tube Defects

- **Management of hydrocephalus**
  - Endoscopic third ventriculostomy
Spina Bifida and Neural Tube Defects

- Pathophysiology and associated disorders
- Chiari II malformation
  - 99% of myelomeningocele have radiographic Chiari II
  - Only symptomatic ones require treatment (30% at 5 years)
  - Responsible for 15-20% of deaths in children with MMC
    - Respiratory failure/arrest
  - Syringomyelia
Spina Bifida and Neural Tube Defects

- Treatment of Chiari II malformation
Current management of spina bifida

- Secondary management
  - Relatively recent: now that these children survive long-term
  - The most difficult – chronic vigilance
  - CNS monitoring:
    - VP shunt management
    - Management of tethered cord (10%)
  - Physical therapy evaluation/motor function of lower extremities
  - Preventive medicine – insensate lower body
  - Psychological support
Spina Bifida and Neural Tube Defects

- **Current management of spina bifida**
  - Secondary management
    - Management of tethered cord
      - Second detethering surgery for decline in function and/or before correction of scoliosis
• Which organ systems does it affect?
  ○ Neuro-motor
  ○ Neurodevelopmental, hydrocephalus, CNS development
Spina Bifida and Neural Tube Defects

- **Which organ systems does it affect?**
  - Neuro-motor
  - Neurodevelopmental, hydrocephalus, CNS development
  - Urogenital
  - Gastrointestinal
    - Gastroesophageal reflux disease (GERD)
    - Constipation
    - More commonly: incontinence
    - Other
  - Variability in severity for all systems (GI specifically)
Peripheral effects of open neural tube defect

- Exposed spinal cord during gestation
- (Progressive?) damage to the exposed neural tube
- Variable paresis, urine & stool incontinence
- CSF leak into amniotic cavity
  - Basis for prenatal testing: leakage of alpha-fetoprotein (AFP)
  - Increased concentration in the amniotic fluid (amniocentesis)
  - Maternal Serum AFP (MSAFP) elevated as well
  - False-positives: any other cause of AFP leakage: gastroschisis
• Peripheral effects of open neural tube defect
  ○ Exposed spinal cord during gestation
  ○ (Progressive?) damage to the exposed neural tube

• Could spina bifida be cured – or even prevented?
• **Embryology of spina bifida – can it be prevented?**
  - **Progressive development theory**
    - Is only one theory – and the most simplistic one
    - Prolonged in utero exposure of the neural tube leads to
      - Chronic leakage of CSF
      - Gradual siphoning and hindbrain herniation
      - Increased risk of hydrocephalus
      - Progressive damage to the neural placode
      - Progressive peripheral nerve damage
        - Lower extremity function
        - Sphincter function
Management of children with spina bifida in the age of fetal intervention

• Spina bifida – can it be diagnosed in utero?
  ○ Ultrasound
    ▪ Spinal defect
    ▪ “Lemon” sign: abnormally shaped skull (head circumference)
    ▪ “Banana” sign: abnormally shaped cerebellum
    ▪ Hydrocephalus
Management of children with spina bifida in the age of fetal intervention

- **Spina bifida – can it be diagnosed in utero?**
  - Magnetic Resonance Imaging
Management of children with spina bifida in the age of fetal intervention

- **Animal experiments – Fetal sheep**
  - Creation of a neural tube defect in a mid-gestation lamb:
    - Leads to phenotype resembling clinical spina bifida
    - Causes hind limb paralysis
    - Causes hydrocephalus

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*In utero* surgery rescues neurological function at birth in sheep with spina bifida

Management of children with spina bifida in the age of fetal intervention

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  - Creation of a neural tube defect in a mid-gestation lamb:
    - Leads to phenotype resembling clinical spina bifida
    - Causes hind limb paralysis
    - Causes hydrocephalus
  - Closure of the defect in utero:
    - Corrects all these problems

*Meuli M et al, Nature Medicine 1995*
Animal experiments – Fetal sheep

- Creation of a neural tube defect in a mid-gestation lamb:
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  - Causes hind limb paralysis
  - Causes hydrocephalus

- Closure of the defect in utero:
  - Corrects all these problems

- Caveat: because this is a surgical created, then corrected defect, it may not be the same as the clinical syndrome
Management of children with spina bifida in the age of fetal intervention

- **Animal experiments – better models?**
  - Mouse models: loss of grainyhead-like (Grhl) gene function:
    - Grhl-3 mutation: ct (curly-tail) mouse
    - Grhl-2 mutation: Axd (axial defects) mouse
Management of children with spina bifida in the age of fetal intervention

- Fetal surgery for spina bifida: from sheep to man
  - Proof of concept in animal model
Management of children with spina bifida in the age of fetal intervention

- Fetal surgery for spina bifida: from sheep to man
  - Proof of concept in animal model
  - Progress in fetal surgery for other indications

Luks FI et al, J Pediatr Surg 1993
Management of children with spina bifida in the age of fetal intervention

- Fetal surgery for spina bifida: from sheep to man
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    - Endoscopic fetal surgery for Twin-to-twin Transfusion Syndrome
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    - 2/4 survivors – technique abandoned

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    - 2/4 survivors – technique abandoned
  - Early 2000: anecdotal, then non-randomized series
    - Vanderbilt, CHOP, UCSF
    - In utero repair is feasible
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  - Early 2000: anecdotal, then non-randomized series
    - Vanderbilt, CHOP, UCSF
    - In utero repair is feasible
    - Possible improvement over postnatal repair? Less hydrocephalus?
    - Final conclusion: it does NOT improve motor function
**Management Of Myelomeningocele Study: The MOMS trial**

- **Started in 2003**
  - Randomized to 3 prenatal centers or postnatal R/
  - Goal: 100 patients/arm
  - Prenatal closure at 19-25 weeks
  - All deliveries in a MOMS center
    - Vanderbilt, Nashville
    - University of California San Francisco
    - Children’s Hospital of Philadelphia
- **Hypothesis:**
  - Fetal repair delays hydrocephalus, prevents Chiari II
  - Not: Better chance of walking!
Management Of Myelomeningocele Study: The MOMS trial

- **Started in 2003**
  - Was supposed to take only 3 years
  - By 2010: Still only 140 patients recruited (of 200 needed)
  - Late 2011: Study suddenly stopped at 85% recruitment
    - Why? Because of better-than-expected results!

New York Times 2011
## 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>Moderate or severe</td>
<td>25</td>
<td>67</td>
<td></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>

### 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>
</tbody>
</table>

Management Of Myelomeningocele Study: The MOMS trial

## Complications

<table>
<thead>
<tr>
<th>Neonatal complications</th>
<th>Fetal</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>2.38</td>
<td>3.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory distress (%)</td>
<td>21</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean GA at birth (wk)</td>
<td>34.1</td>
<td>37.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Born &lt;30 wk (%)</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Born 30-34 wk (%)</td>
<td>33</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>


Management Of Myelomeningocele Study: The MOMS trial
### Complications (%)

<table>
<thead>
<tr>
<th>Pregnancy complications</th>
<th>Fetal</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligohydramnios</td>
<td>21</td>
<td>4</td>
<td>0.001</td>
</tr>
<tr>
<td>PROM</td>
<td>46</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uterine wound:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact and healed</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very thin</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some dehiscence</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Management of children with spina bifida in the age of fetal intervention

- In utero repair of spina bifida: how is it done?
- Maternal and fetal anesthesia
  - General anesthesia
  - Uterine relaxation
    - Inhalation anesthesia
  - Preserved placental circulation
  - Arterial line
  - Epidural for analgesia
  - MgSO$_4$ for CP prevention
  - Steroids (prematurity)
Management of children with spina bifida in the age of fetal intervention

- In utero repair of spina bifida: how is it done?
- Multidisciplinary team approach
  - Maternal Anesthesia
  - Maternal-Fetal Medicine
  - Pediatric Surgery
  - Pediatric Neurosurgery
  - Pediatric Plastic Surgery
  - Neonatology
Management of children with spina bifida in the age of fetal intervention

- In utero repair of spina bifida: how is it done?
- Wide maternal laparotomy
  - Full exposure of the uterus
Management of children with spina bifida in the age of fetal intervention

- In utero repair of spina bifida: how is it done?
- Partial exteriorization of the uterus
  - Ultrasound-guided mapping of the placenta, fetus
  - Stapled hysterotomy (preservation of membranes)
Management of children with spina bifida in the age of fetal intervention

- In utero repair of spina bifida: how is it done?
- Exposure of the neural tube defect
In utero repair of spina bifida: how is it done?
Exposure of the neural tube defect
Meticulous, but rapid closure
### Management of children with spina bifida in the age of fetal intervention

#### Postnatal repair *versus* Prenatal repair?

<table>
<thead>
<tr>
<th>Postnatal repair</th>
<th>Prenatal repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Separation of placode from epithelium</td>
<td>A. Same, but much faster</td>
</tr>
<tr>
<td>- “Trimming of the placode”</td>
<td>- Healthy cord without epithelium, inflammation or infarction</td>
</tr>
<tr>
<td>- Use of surgical microscope</td>
<td>- No trimming of the placode</td>
</tr>
<tr>
<td>B. Preservation of placode, vascular supply</td>
<td>B. Same, but <em>no</em> significant dural vascular supply (“bloodless” placode)</td>
</tr>
<tr>
<td>- “Meticulous” hemostasis and microdissection</td>
<td>- No use of microscope</td>
</tr>
<tr>
<td>- Use of surgical microscope</td>
<td></td>
</tr>
<tr>
<td>C. Anatomical reconstruction</td>
<td>C. No!</td>
</tr>
<tr>
<td>- Prevention of re-tethering, ischemia, CSF leak, infection</td>
<td>- Only attempt to approximate dura and skin</td>
</tr>
<tr>
<td>- Sufficient dissection of dural layer to prevent ischemia</td>
<td>- Occasional dural/skin substitute</td>
</tr>
<tr>
<td>- Myofascial skin/subcutaneous fat dissection, preparation and closure are important!</td>
<td>- Counsel parents: fetal repair is <em>not</em> formal and anatomic repair</td>
</tr>
<tr>
<td></td>
<td>- Second repair after birth</td>
</tr>
<tr>
<td></td>
<td>- Close watch for tethering</td>
</tr>
</tbody>
</table>
Management of children with spina bifida in the age of fetal intervention

• The post-MOMS era
  ○ How has it changed the management of spina bifida?
  ○ Increasing number of centers offer the procedure
  ○ Strict selection criteria
    ▫ Not for all lesions or all gestational ages (window)
    ▫ Maternal physiology and phenotype
    ▫ Psychological evaluation
    ▫ Not an alternative to termination
    ▫ No guaranteed results
    ▫ Maternal complications
    ▫ Mandatory C/Section for this and future pregnancies
Management of children with spina bifida in the age of fetal intervention

**MOMS II**
- Further analysis of the results in the initial cohort
  - It improves motor function
- Does it improve GERD?
  - No real evidence (25% if shunted, v. 8% if not shunted)
- Does it improve continence?
  - No word yet – but the answer appears to be “no”
- Does it improve cognitive outcome?
  - Unclear – but encouraging results at 30 months...
- Does it prevent/ Improve Tethering?
  - No word yet – but appears to be the opposite

Danzer E et al, Neuropediatrics 2008
Conclusions:

- Postnatal treatment remains the gold standard
- Selected patients may benefit from prenatal intervention
- Primary goal is rapid closure of the defect
- Early treatment of hydrocephalus and Chiari malformation
- Secondary treatment is long and difficult
  - Neurological effects
  - Urogenital effects
  - Gastrointestinal effects
  - Psychological support

Management of children with spina bifida in the age of fetal intervention