Fetal Surgery: Where are we now?

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Learning Objectives

- To review the various methods of fetal interventions
- Review the risks versus benefits of the various types of fetal interventions
- Describe the fetal conditions currently amenable to in utero therapy

Challenges of Delivering Fetal Therapy

- Diagnostic Challenges
  - Identify Fetal Patient
- Treatment Challenges
  - Efficacy
  - Surgical Technique
  - Fetal Safety
  - Maternal Safety
  - Timing of Delivery
  - Delivery Method
- Ethical Challenges
### Fetal Therapy Ethical Issues

- **Maternal**
  - Maternal risks vs. benefits
  - Sensitivity to psychosocial aspects of pregnancy and maternal vulnerability
- **Fetal**
  - Risk of procedure related complications versus natural history of disease
- **Societal Costs**

### CHLA-USC Fetal Therapy Ethics Committee

- Provide ethical oversight for proposed fetal therapy cases

### Composition

- **Ethicists**
  - Advise the committee on the ethical principles involved in each case
- **Neonatologist**
  - Represents the interests of the fetus/neonate
- **Obstetrician**
  - Represents the interests of the mother

### Fetal Therapy

1. Open Fetal Surgery
2. Operative Fetoscopy
3. Shunt Procedures
4. Needle
5. Medical Therapy

**Level of Invasiveness**
Open Fetal Surgery

- Examples of open fetal surgery
  - Myelomeningocele
  - MOMS (Management of Myelomeningocele Study)

Operative Fetoscopy
Operative Fetoscopy

- Example of fetoscopic surgical treatments
  - Twin-twin transfusion syndrome (TTTS)
    - Laser photocoagulation of communicating vessels
    - Selective intrauterine growth restriction in monochorionic twins
    - Laser photocoagulation of communicating vessels
  - Monochorionic twins with discordant anomalies
    - Umbilical cord occlusion
    - TRAP sequence
    - Umbilical cord occlusion
    - Lower urinary tract obstruction
    - Ablation of posterior urethral valve
    - Mild amniotic bands
    - Lysis of amniotic bands
    - Congenital diaphragmatic hernia
    - Tracheal plug
**Twin-Twin Transfusion Syndrome (TTTS)**

- High perinatal mortality
  - Up to 95% in conservatively managed patients with TTTS diagnosed during the midtrimester
- High risk of long-term morbidity in untreated cases
- Relatively common
  - 10-15% of monochorionic twins
  - 1 in 3200 pregnancies (or 1:1600 fetuses)

**Pathophysiology**

- Fetuses structurally normal
- Unbalanced intertwin transfusion along placental vascular anastomoses
- Anastomoses present in 95-100% of monochorionic placenta
  - Two types
    - Superficial
      - Arterio-arterial (AA)
    - Venous-venous (VV)
    - Deep
      - Arterio-venous (AV)

**Monochorionic Placenta**

![Monochorionic Placenta Image]
AV Anastomosis

The Swaddled Twins

De Wikkellkinderen (The Swaddled Twins), Artist unknown, painting dated April 7, 1617. Currently housed in The Muiderslot, Amsterdam.

TTTS - Diagnosis

- Amniotic Fluid Discordance
  - Recipient
    - Maximum vertical pocket greater than or equal to 8.0 cm
  - Donor
    - Maximum vertical pocket less than or equal to 2.0 cm
TTTS - Treatment

- Expectant management
- Termination of pregnancy
- Serial amnioreduction
- Selective laser photocoagulation of communicating vessels
- Umbilical cord occlusion

TTTS - Treatment Outcomes

- Eurofoetus Trial
  - Senat, NEJM, 2004
  - Study of unstaged midtrimester TTTS prospectively randomized to serial amnioreduction versus laser surgery

Laser Surgery

- Laser Surgery
## TTTS - Treatment Outcomes

- Eurofoetus Trial
  - Pretrial power analysis: n of 340
  - Study interrupted by independent monitoring team because significant survival improvement shown at n of 142

## TTTS - Eurofoetus Trial

<table>
<thead>
<tr>
<th></th>
<th>Serial A/C (n=70)</th>
<th>Laser (n=72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (%)</td>
<td>51.4%</td>
<td>76.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>GA at Delivery (wks)</td>
<td>29.0 wks</td>
<td>33.3 wks</td>
<td>0.004</td>
</tr>
<tr>
<td>Neurologic (cystic PVL)</td>
<td>14.5%</td>
<td>5.6%</td>
<td>0.02</td>
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</tbody>
</table>

Outcome measure: Neurologic Injury at 6 months of age

- Amnioreduction group
  - 19% of survivors had neurologic injury
- Laser group
  - 7% of survivors had neurologic injury
TTTS
- Conclusion

- Eurofoetus Trial
  - “Endoscopic laser coagulation of chorionic plate vascular anastomoses is a more effective first line treatment of severe twin-to-twin transfusion syndrome before 26 weeks’ than serial amniodrainage.”

TTTS
- NIH Sponsored Trial

- NIH Trial
  - Prospective randomized clinical trial of amnioreduction versus selective fetoscopic laser photocoagulation for twin-twin transfusion syndrome
    - Amnioreduction group (17 centers - including USC)
    - Laser group (3 centers - UCSF, CHOP, Cincinnati Children’s)

TTTS
- NIH Sponsored Trial

- NIH Trial Study Design
  - Primary outcome - 30 day postnatal survival
  - Amnioreduction performed and patients with persistent TTTS randomized to serial amnioreduction versus laser therapy
  - N = 42 (21 in each arm)
**TTTS - NIH Sponsored Trial**

- **NIH Trial Outcomes**
  - At least 1 survivor:
    - Serial Amnioreduction - 75%
    - Laser - 65% (p=NS)
  - Recipient survival in Quintero Stage III and IV TTTS cases
    - Serial Amnioreduction - 67%
    - Laser - 13% (p<0.03)

- **NIH Trial Conclusion**
  - “Intervention before TTTS becomes advanced may be necessary to improve survival.”

**CHLA-USC IMFH Experience**

- March 2006 - April 2008
  - 101 patients met criteria for TTTS
    - 1 opted for TOP
    - 1 opted for intentional septostomy
    - 99 underwent SLPCV
  - Perinatal outcome (30-day survival)
    - 91% one or two twin survival
    - 72% dual survival

Chmait, Kahn, Benirschke et. al. Manuscript submitted for publication.
TTTS
- Metaanalysis

- Amnioreduction vs. Laser
  - 10 articles provided 611 TTTS cases
  - 4 articles directly compared the two treatment modalities
- Results
  - Fetuses undergoing laser had higher survival (OR 2.0 [1.5–2.8]) and lower neurologic morbidity (OR 0.2 [0.1–0.3])


Long-term Neurodevelopmental Outcome after Laser for TTTS

- 167 children post-laser for TTTS enrolled
  - Median age 3 years 2 months
- Cases performed between 1997 - 1999
  - Many surgical improvements have subsequently been developed
- Two neurodevelopmental standardized tests used to assess outcome
  - 10/167 (6.2%) with severe neurologic deficits


TTTS vs. SI UGR

- Weight discordance
- Amniotic fluid discordance
### Congenital Diaphragmatic Hernia

- CDH occurs in 1:3000 pregnancies
- 84% left-sided, 13% right-sided, 2% bilateral.
- 30% have associated structural, chromosomal, or syndromic abnormalities. These fetuses have less than a 15% survival rate.

### Congenital Diaphragmatic Hernia

- Perinatal survival 40-60%, although as high as 85% in some centers
  - Correlated with Lung-to-Head Ratio (LHR = Rt lung/ head circumference)
  - LHR < 1.0, left sided, liver up associated with less than 33% survival

### Congenital Diaphragmatic Hernia

- Secondary Pulmonary Pathology
  - Fewer alveoli, thickened alveolar walls, increased interstitial tissue, markedly diminished alveolar airspace and gas-exchange surface area
  - Parallel to the airway changes, pulmonary vasculature is abnormal, with a reduced number of vessels, advential thickening, medial hyperplasia, and peripheral extension of the muscle layer into the smaller intra-acinary arterioles
**Congenital Diaphragmatic Hernia**

- Pathologic pulmonary system leads to:
  - Pulmonary hypoplasia
  - Ventilatory insufficiency
  - Variable degrees of persistent pulmonary hypertension

**In utero treatment via tracheal occlusion**
- CAOS - chronic airway obstruction syndrome
- Experimental basis of tracheal occlusion via sheep models as method to improve lung growth and reverse vascular changes
  - Oligo-macroalveolar development
- U.S. experience using tracheal plug
  - Hysterotomy, fetoscopic balloon tracheal occlusion showed no benefit compared to expectant management

**Recent European preliminary results** (Deprest 2004)
- Candidates - LHR < 1.0, left sided, liver up associated with less than 33% survival
- Fetoscopic endoluminal tracheal occlusion
  - Plug at 26-28 weeks
  - Unplug at 34 weeks
- Perinatal survival 60% (90% in those unplugged at 34 weeks) versus 8% in contemporary controls
Congenital Diaphragmatic Hernia

- Tracheal plug

Shunt Procedures

- Examples of large caliber needle and/or shunt procedures
  - Type I CCAM or Pleural Effusions with Hydrops
    - Thoracoamniotic Shunts
  - Lower Urinary Tract Obstruction
    - Vesicoamniotic Shunt

Cystic Chest Mass with Hydrops

- Lesion type
  - Congenital cystic adenomatoid malformation (CCAM) of the lung
  - Bronchopulmonary sequestration (BPS)
- Literature – recent review
  - Fetuses with CCAM or BPS with hydrops treated with drainage (thoracoamniotic shunt or thoracocentesis) versus untreated had a significant increased perinatal survival rate (OR 19.3, 95% CI 3.7–101.3, p=0.0003)

**Congenital Cystic Adenomatoid Malformation**

- Hamartoma of terminal respiratory bronchioles
- 80-95% are unilobar
- Aneuploidy associated in <1%
  - most common abnormal karyotype is trisomy 21

**CCAM with Secondary Hydrops**

- CHLA-USC IMFH Case Report
  - Ms. MF, 40 yo seen at 25+2 wks
  - Referred for a chest mass and hydrops
  - No abnormalities seen on 16+ wk scan
  - Prior amniocentesis showed normal karyotype

**Pre-Operatively...**
Thoracotomy and Lobectomy

Postop Resection Day 10

6 months old
**Lower Urinary Tract Obstruction**

- Posterior urethral valves (24%)
- Urethral atresia (20%)
- Prune-belly syndrome (16%)
- Obstructing ureterocele
- Megacystis-microcolon-hypoperistalsis syndrome
- Others

**LUTO Assessment**

- Sonogram
  - Amniotic fluid volume
  - Amnioinfusion may be necessary
  - Characterize kidneys
  - Other malformations
- Rapid Karyotype
- Kidney evaluation
  - Multiple bladder taps q 24-48 hours
  - Assess kidney function via urinary Na, Cl, Osm, Ca, B2 microglobulin

**LUTO Treatment**

**Vesicoamniotic Shunt**
Obstructive Uropathy: Long-Term Outcomes

Lancet 1999

Renal Outcome Post-Fetal Shunt (age>2yrs)

- Normal: 6/14 (43%)
- Renal Insufficiency: 3/14 (21%)
- ESRD: 5/14 (36%)


Obstructive Uropathy: Long-Term Outcomes

Clinical outcomes of male fetuses who had vesicoamniotic shunting for LUTO with oligo/anhydramnios

- 18 patients
- Mean GA at diagnosis: 19.4 weeks
- Mean GA at delivery: 34.6 weeks
- Serial prognostic vesicocenteses
  - 13/18 good prognosis
  - 2/18 borderline prognosis
  - 3/18 poor prognosis
    - Maximum 2 values above threshold
    - 3 or more values above threshold


Obstructive Uropathy: Long-Term Outcomes

Diagnosis
- Posterior urethral valves: 7/18
- Prune belly syndrome: 7/18
- Urethral atresia: 4/18
- Mean age of follow up: 5.8 years

Obstructive Uropathy: Long-Term Outcomes

- **Renal function**
  - 8 acceptable renal function ($Cr_{cr} > 70$ mL/min)
  - 4 mild renal insufficiency ($Cr_{cr} > 70$ mL/min that did not require renal replacement therapy)
  - 6 required dialysis and eventual renal transplant

- **Bladder function**
  - 11 normal, spontaneous voiding
  - 6 require catheterization
  - 1 with vesicostomy


- **Height/weight < 25% (9)**
- **Persistent respiratory problems (8)**
  - Asthma and frequent infections
  - Limitation in daily activity (2)
- **Musculoskeletal problems (9)**
- **Frequent UTI (9)**

- **Health-related quality of life similar to healthy child population**


Fine Needle Procedures

- **Examples of fine needle procedures**
  - Severe Fetal Anemia or Thrombocytopenia
  - IUT
  - Iatrogenic Preterm Premature Rupture of Membranes
  - Amniopatch
Amniopatch for iPROM

- Amniopatch
  - Minimally invasive technique to seal ruptured membranes secondary to a previous invasive procedure
- Iatrogenic premature rupture of fetal membranes (iPROM)
  - Up to 1% genetic amniocenteses
  - 5-8% operative fetoscopy

Methods
- 22 gauge needle
- Amniotic fluid withdrawn for septic profile
- Infusion
  - ½ unit platelets
  - 1 unit cryoprecipitate

Amniopatch for iPROM

Amniopatch for iPROM

Amniopatch for iPROM

Amniopatch for iPROM

Amniopatch for iPROM
Amniopatch for iPROM

  - 20 patients (heterogeneous group)
    - 7 genetic amniocentesis
    - 7 laser surgery for TTTS
    - 3 in utero therapy for lower urinary tract obstruction
    - 1 chorionic villus sampling
    - 2 umbilical cord occlusions
  - 2 patients interrupted their pregnancies and were excluded from further analysis
    - 1 trisomy 18
    - 1 intra-amniotic infection

Amniopatch for iPROM

- Results (Quintero, Chmait, et al)
  - Sealed membranes in 72% (13/18)
  - Median/range gestational age at delivery in sealed versus unsealed patients
    - Sealed: 35 weeks (18.9-41.0)
    - Unsealed: 20.8 weeks (19.6-21.7)
  - Perinatal survival higher in sealed versus unsealed patients (77% versus 0%, p=.006)

Amniopatch for iPROM

- Conclusion (Quintero, Chmait, et al)
  - iPROM successfully treated in 70% of cases
  - Lack of membrane sealing associated with a poor perinatal outcome
  - Multicenter prospective RCT of expectant management versus amniopatch is being organized
Iatrogenic Detachment of Fetal Membranes and Role of Interim Amniopatch

- Membrane detachment is known complication of amniocentesis
- Operative fetoscopy may be hindered or made altogether impossible by this complication


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Iatrogenic Detachment of Fetal Membranes and Role of Interim Amniopatch

- Study of TTTS patients post amniocentesis complicated by membrane detachment
  - 26 of 322 (8%) with TTTS treated initially with amnioreduction had membrane detachment
  - 12 patients opted to undergo amniopatch of which 8 had resealing of membranes (66%)


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Medical Therapy

- Examples of transplacental fetal therapy
  - Congenital adrenal hyperplasia
    - Dexamethasone
  - Alloimmune thrombocytopenia
    - Dexamethasone
    - Intravenous immunoglobulin
  - Fetal supraventricular tachycardia
    - Digoxin; Flecainide
  - Heart block
    - Beta mimetics
CHLA-USC Fetal Therapy
Program at HP

- Needle/Shunt Procedures
  - Diagnostic cordocentesis
  - Intraventricular transfusion
  - Isoinmunization
  - Allimmune thrombocytopenia
  - Thoracoamniotic shunt
  - Treated pleural effusions
  - Large Type I CCAM
  - Veseoamniotic shunt
  - Lower urinary tract obstruction
  - Amniopatch
  - Iatrogenic previable premature rupture of membranes
- Operative Fetoscopy
  - Twin-twin transfusion syndrome
  - Selective intrauterine growth restriction in monochorionic twins
  - TRAP (acardiac) twins
  - Monochorionic twins with lethal discordant anomaly
  - Lower urinary tract obstruction
  - Mild amniotic bands
- Future Fetal Therapies
  - Congenital diaphragmatic hernia
  - Congenital heart defects
  - Gene therapy

Fetal Therapy Program Reunion
March 30, 2008

Questions