Advances in Fetal Therapy
What’s New

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Fetal Care Center Of Cincinnati
Cincinnati Children Hospital
University of Cincinnati
Ohio USA
Rational For fetal Therapy

1-The life of fetus is at risk as it develops in utero.
   - Progression of the disease will result in fetal demise
     - TTTS
     - Rapid growing tumors
   - Hydrops fetalis is an end point that may signal the need for fetal intervention

2-Treating the disease earlier in gestation may allow for better growth and development, and less subsequent disability
   - MMC
   - LHFH

3-Diseases will not allow for successful transition to extra-uterine life
   - Airway obstruction
Fetoscopic indications

- Twin–twin transfusion syndrome
- Twin-reversed arterial perfusion (TRAP) cord coagulation vs RFA
- Fetal tracheal balloon occlusion in diaphragmatic hernia
- Fulgurization of posterior urethral valves
- Tracheal decompression in fetal laryngeal atresia
- Spina bifida repair
Ex Utero Intrapartum Treatment

EXIT to Airway
CHASES
Neck masses
Micrognathia

EXIT to ECMO
High risk CDH
EXIT to Cardiac Cath
Hypoplastic left heart syndrome with restrictive atrium

EXIT to resection
CPAM/CCAM mediastinal & pericardial masses
Recommended Fetal Interventions and Surgeries

**Level I Evidence**
- Laser ablation for TTTS
- FETO for CDH
- VAS for LUTO
- Open MMC Repair

**Level II or III Evidence**
- Fetoscopic MMC Repair
- Amniotic Band Syndrome
- Fetal Lung Mass
- TAPS/ TRAP
- Fetal Cardiac Intervention
- Selective Feticide
- Others
Background: TTTS

- Most common complication of monochorionic twinning
- 15% (4-35%) of all monochorionic twin gestations in U.S.
- 17% of all mortality in twins
- 80-100% mortality—untreated
  - Death of one twin:
    - 12% subsequent death of co surviving twin
    - 18% neurologic damage of the co-twin
- Pathophysiology: not entirely clear!
Twin to Twin Transfusion Syndrome (TTTS)

SMFM, AJOG 2013.
Donor

¬ ▼ blood volume, colloids
¬ hypovolemia
¬ ▼ urination
¬ ▲ RAS activation
¬ Œ A-V transfer

Recipient

¬ ▲ blood volume, colloids
¬ hypervolemia
¬ ▲ urination
¬ ▼ RAS activity
  – A-V reception

Adapted from Van Den Wijngaard et.al., Prenat Diagn 2008; 28
Quintero Staging

- **Stage I**
  - Oligo-/polyhydramnios in recipient/donor

- **Stage II**
  - Stage I PLUS absent bladder in donor twin

- **Stage III**
  - Critical Doppler changes:
    - Absent/reverse diastolic flow in UA
    - Reverse flow in DV, UV pulsation

- **Stage IV**
  - Hydrops in either twin (usually the RT)

- **Stage V**
  - Demise of one twin
SMFM Algorithm for Screening of TTTS

**SMFM Clinical Guideline**

**Figure 5**
Algorithm for screening for TTTS

- **MCDA pregnancy**
  - First trimester:
    - Confirm monochorionic, diamniotic placentation
    - NT screening
  - ~16 weeks:
    - Start ultrasound surveillance with MVP in each sac, and fetal bladder in each fetus, every 2 weeks, until delivery

**MVP >2cm and <8cm in each sac**
- Yes: Continue ultrasound surveillance every 2 weeks
- No: MVP <2cm in 1 sac and MVP >8 cm in other sac: Diagnosis = TTTS

See Figure 10

Twin to Twin Transfusion Syndrome – Can we predict?
Twin to Twin Transfusion Syndrome – Can we predict?

**CONCLUSIONS**  Discordance in NT of 20% or more is found in about 25% of monochorionic twins and in this group the risk of early fetal death or development of severe TTTS is more than 30%. If the discordance is less than 20% the risk of complications is less than 10%.
Twin to Twin Transfusion Syndrome
Laser ablation vs. amnioreduction

Endoscopic Laser Surgery versus Serial Amnioreduction for Severe Twin-to-Twin Transfusion Syndrome

Marie-Victoire Senat, M.D., Jan Deprest, M.D., Ph.D., Michel Boulvain, M.D., Ph.D., Alain Paupe, M.D., Norbert Winer, M.D., and Yves Ville, M.D.

CONCLUSIONS
Endoscopic laser coagulation of anastomoses is a more effective first-line treatment than serial amnioreduction for severe twin-to-twin transfusion syndrome diagnosed before 26 weeks of gestation.
Twin to Twin Transfusion Syndrome
Laser ablation
<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>Amnioreduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival of one fetus</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>Survival of both fetuses</td>
<td>36%</td>
<td>26%</td>
</tr>
<tr>
<td>Survival of at least one fetus</td>
<td>76%</td>
<td>51%</td>
</tr>
<tr>
<td>GA at delivery</td>
<td>33.3</td>
<td>29.0</td>
</tr>
<tr>
<td>Alive w/o neurologic problems</td>
<td>52%</td>
<td>31%</td>
</tr>
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</table>

## Twin to Twin Transfusion Syndrome
### Laser ablation vs. amnioreduction

<table>
<thead>
<tr>
<th></th>
<th>Laser Senat 2004</th>
<th>Laser 2014</th>
<th>Cincinnati 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival of both fetuses</strong></td>
<td>36%</td>
<td>65-70%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Survival of at least one fetus</strong></td>
<td>76%</td>
<td>85-90%</td>
<td>93%</td>
</tr>
</tbody>
</table>

*Chmait et al. AJOG, 2011.*
https://www.youtube.com/watch?v=G3y6MbZitLA&feature=youtu.be
Twin to Twin Transfusion Syndrome
Role of Fetal Echocardiography
Cardiac Sequelae: Recipient Twin

- Early Hypertrophy
- Late Hypertrophy
- Further hypertrophy
- Fibrosis? Apoptosis?
- Diastolic Dysfunction
- Systolic Dysfunction
- Impaired relaxation
- Elevated filling pressures
- HYDROPS
- Stroke volume
- Cardiac output

- Angiotensin II
- ET-1
- Hypertension
- Volume Overload

Cardiac Remodeling

Volume Output
Quintero Stage and Cardiomyopathy in TTTS

Ultrasound Obstet Gynecol 2007; 30: 965–971
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/uog.5211

Early manifestations and spectrum of recipient twin cardiomyopathy in twin–twin transfusion syndrome: relation to Quintero stage

E. MICHELFELDER*,†, W. GOTTLEIBSON*,†, W. BORDER*,†, M. KINSEL*, W. POLZIN†‡, J. LIVINGSTON†§, P. KHOURY* and T. CROMBLEHOLME†¶

*Division of Cardiology, †Fetal Care Center of Cincinnati and ‡Department of Surgery, Cincinnati Children’s Hospital Medical Center, ¶Division of Maternal-Fetal Medicine, Good Samaritan Hospital and §University of Cincinnati College of Medicine, Cincinnati, OH, USA
# Cardiac Findings in TTTS: Recipient Twin

<table>
<thead>
<tr>
<th>Cardiac Findings</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
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<tbody>
<tr>
<td>Ventricular hypertrophy</td>
<td>57%</td>
<td>64%</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>AVVR</td>
<td>14%</td>
<td>28%</td>
<td>45%</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; Moderate tricuspid regurgitation</td>
<td>7%</td>
<td>21%</td>
<td>28%</td>
<td>100%</td>
</tr>
<tr>
<td>Abnormal RV MPI</td>
<td>30%</td>
<td>64%</td>
<td>63%</td>
<td>n/a</td>
</tr>
<tr>
<td>Abnormal LV MPI</td>
<td>55%</td>
<td>70%</td>
<td>44%</td>
<td>100%</td>
</tr>
<tr>
<td>Ventricular systolic dysfunction</td>
<td>21%</td>
<td>21%</td>
<td>42%</td>
<td>100%</td>
</tr>
</tbody>
</table>

From Michelfelder et.al., Ultrasound Obstet Gynecol 2007; 30
Cardiac Assessment in TTTS

- Huhta et al. Cardiovascular Profile Score
- Michelfelder et al. CVPS
- Shah AD, et al, CVPS
  J Am Soc Echocardiogr 2008
- Rychik et al. Cardiovascular Score
- Habli et al. Cincinnati staging system

- TTTS has important and direct effects on the cardiovascular system of the recipient twin affecting
  - Preload
  - Cardiac function
  - Afterload.
Cincinnati Modification of Quintero TTTS Staging

Stage I
Stage II
Stage III
   IIIA  Mild cardiomyopathy
   IIIB  Moderate cardiomyopathy
   IIIC  Severe cardiomyopathy
Stage IV
Stage V
Cincinnati Staging System

- Guiding the need for SFLP
- Impact survival
- Progression of disease
- Pre-procedural administration of Nifedipine to reduce afterload and improve recipient outcome.
Twin-Twin Transfusion Syndrome

Selective Fetoscopic Laser Photocoagulation

- Role for adjunctive medical therapy?
Case Control Observational Study of Nifedipine in TTTS-Cardiomyopathy

- Consecutive TTTS Nifedipine treated cases
  - 2008-2009
  - Stages IIIA, IIIB, IIIC, IV
  - 20 mg q 6 hours 24-48 hrs pre-SFLP

- 152 TTTS control cases
  - 2005-2007
  - Matched for Cincinnati Stage
  - Matched for gestational age
  - Matched 2:1 when possible
  - Same team, same protocol
Effect of Nifedipine on Survival in TTTS Cardiomyopathy Treated by SLFP

- Significantly improves overall survival
- Significant improvement in recipient survival
- No survival benefit in donors at any stage
- Need prospective randomized trial
TTTS Conclusion Summary

- Early diagnosis as of 11 -13 weeks.
- SMFM guidelines
- Fetal Echo as part of standard evaluation
- Standard of care Treatment is SFLP
- Procardia as adjunct Medical therapy
“I don’t mind the night shift except for one thing, I am afraid of the dark!”
Recommended Fetal Interventions and Surgeries

- Level I Evidence
- Laser ablation for TTTS
- FETO for CDH
Failure of closure of pleuroperitoneal folds during Weeks 4 – 10 post fertilization
1:2200 – 1:5000
2 types:
- Bochdalek (95%): postero-lateral
- Morgagni (5%): anterior retrosternal/peristernal

• 85% Left sided
• 10-15% right sided
• Bilateral is rare

*50% isolated and 50% have other anomalies
*15% aneuploidy, 10% syndromic

*Postnatal: 25-35% mortality
*Prenatal: > 50% mortality

Torfs et al, 1992
CDH Consequences

3 major issues:
- Lung hypoplasia
- Pulmonary hypertension
- Cardiac compression

- Bronchial branching with fewer alveoli
  - Fewer respiratory bronchioles
  - Surface area for gas exchange
  - (ipsilateral / contralateral lung)

- Lung Hypoplasia
- Pulmonary Hypertension

- LV hypoplasia
  - Vascular changes – reduced vasculature; abnormal smooth muscle response

- Diaphragmatic defect
CDH - Spectrum of Disease

5 - 10%
Severe

Severe Fixed Hypoplasia
Inadequate Gas Exchange

Fetal Surgery?

75 - 85%
Moderate

Fixed Hypoplasia with Reversible Pulmonary HTN
Marginal Gas Exchange
Clinical Lability

Ventilation
ECMO
HFV?
Nitric Oxide?
Liquid Ventilation?

10 - 5%
Mild

Mild Hypoplasia
Good Gas Exchange

Cincinnati Children's
Lung-to-head ratio (LHR)

Mild: >1.4
Moderate: 1.0-1.4
Severe: < 1.0

Liver herniation
Yes
No

Outcome predictors for Congenital Diaphragmatic Hernia

Mri volumetric assessment
O/E- TLV
PPLV

Predict the size of the lungs

Zamora et al, 2014
CDH Prognostic Criteria
Fetal Liver Herniation
Outcome predictors for Congenital Diaphragmatic Hernia

Lung volume

Lung-to-head ratio (LHR)

- >1.4: Mild
- 1.0-1.4: Moderate
- <1.0: Severe

Liver herniation

- Yes
- No

Predict the size of the lungs

Zamora et al, 2014
SEVERE CONGENITAL DIAPHRAGMATIC HERNIA

PRENATAL SONOGRAPHY
Transversal Cut at 4 cardiac chambers level

LUNG - HEAD RATIO (LHR)

\[
LHR = \frac{\text{CONTRALATERAL PULMONARY AREA (AxB)}}{\text{CEPHALIC PERIMETER}}
\]
SEVERE CDH

PRENATAL SONOGRAPHY

LHR 0.67
Previous studies have reported that the LHR increases with gestation in both normal fetuses and in those with diaphragmatic hernia.

Consequently, in fetuses with CDH it is preferable to use the observed to expected normal mean for gestation (O/E) LHR.
Outcome predictors for Congenital Diaphragmatic Hernia

Lung volume

Lung-to-head ratio (LHR)

MRI volumetric assessment

O/E LHR- TLV
PPLV

Liver herniation

Predict the size of the lungs

Zamora et al, 2014
Fetal MRI performed on 1.5 T Signa Scanner
All images reviewed by one of four fetal radiologists
Single technician to calculate lung volumes
Lung volumes were calculated by summation of the right and left lung volumes with exclusion of hernia and mediastinal contents

<table>
<thead>
<tr>
<th>Region</th>
<th>Volume (ml)</th>
<th>Average</th>
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<tbody>
<tr>
<td>Left Lung</td>
<td>7.47</td>
<td>75.3 +/- 16.3</td>
</tr>
<tr>
<td>Right Lung</td>
<td>9.69</td>
<td>76.2 +/- 13.1</td>
</tr>
<tr>
<td>Total</td>
<td>17.16</td>
<td></td>
</tr>
</tbody>
</table>

MRI ASSESSMENT OF TOTAL LUNG VOLUME
CDH - Prognostic Criteria

**PPLV**

Percent Predicted Lung Volume (PPLV)

\[
\text{Total Lung Volume} = \frac{\text{Total Thoracic Vol-Mediastinal Vol}}{\text{PPLV}}
\]

Gorincour et al Ultrasound Obstet Gynecol 26: 738-744
McGoon Index (MGI)
Assess risk of pulmonary Hypertension

\[ \text{MGI} = \frac{(A + B)}{C} \]
McGoon Index (MGI)

\[ MGI = \frac{RPA_d + LPA_d}{Ao_d} \]
All prognostic indicators focus on lungare indirect

Poor Indicators severe CDH:
- $LHR<1$
- $PPLV<15$
- $TLV<20$
- Liver position up

Indicator of pulmonary hypertension

Modifed McGoon Index
- $\geq 1.2$ low risk
- $\leq 0.8$ high risk
### CDH-Composite Prognostic Index (CDH-CPI)

<table>
<thead>
<tr>
<th>Genetics</th>
<th>1</th>
<th>0</th>
<th>-1</th>
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<tbody>
<tr>
<td>Karyotype Syndrome</td>
<td>Normal</td>
<td>Mild</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>1</th>
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<th>-1</th>
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<tbody>
<tr>
<td>CHD</td>
<td>None</td>
<td>VSD/ASD/Coarctation</td>
<td>Double outlet heart disease</td>
</tr>
<tr>
<td>LV/RV</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>McGoon</td>
<td>&gt;1.2</td>
<td>&lt;1.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hernia</th>
<th>1</th>
<th>0</th>
<th>-1</th>
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</thead>
<tbody>
<tr>
<td>Sac</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Down</td>
<td>Up</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung</th>
<th>1</th>
<th>0</th>
<th>-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHR</td>
<td>&gt;1</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>PPLV</td>
<td>&gt;15%</td>
<td>&lt;15%</td>
<td></td>
</tr>
<tr>
<td>TLV</td>
<td>&gt;18 mL</td>
<td>&lt;18 mL</td>
<td></td>
</tr>
</tbody>
</table>
CDH-Composite Prognostic Index (CDH-CPI)

Figure 1

Left CDH

% Survival

CDH CPI Score

n=15
<6
33%

n=13
7
46%

n=19
8
79%

n=15
9
93%

n=2
10
100%
Fetal Intervention for CDH

Tracheal Occlusion

Plug the Lung Until it Grows
THE PAST
CDH-OPEN  FETAL SURGERY

TRACHEAL OCCLUSION

CDH
FETENDO (FETal - ENDOscopy)
INCLUSION CRITERIA

- Diagnosis before 26 weeks gestation
- Severe Pulmonary Hypoplasia  LHR < 1
- Hepatic herniation (Liver-up)
- No associated malformations
- Normal Karyotype
- Single Gestation
- No maternal disease
Fetal tracheal occlusion for severe CDH

Percutaneous fetoscopic access
26 - 29 w. GA
Fetal tracheal occlusion for severe CDH
Fetal tracheal occlusion for severe CDH

Detachable endotracheal balloon

Volume Balloon Max.:
Max. Balloon Volume:
Max. volumen del balón:

V : 0.60 ml

20 mm
7 mm

GOLDBAL2
FETOSCOPIC TRACHEAL OCCLUSION
endotracheal balloon
Fetal tracheal occlusion for severe CDH

PRENATAL SONOGRAPHY PLUG

PLUG

TRACHEA

Distance:
1 DIST = 2.25 cm
2 DIST = 0.71 cm
3 DIST = 1.87 cm
After PLUG

Does the lung really grow?

EUROPEAN COLLABORATIVE STUDY FOR SEVERE CDH INTRAUTERINE TREATMENT
Fetal tracheal occlusion for severe CDH

20 days after PLUG

LHR 0.67  →  LHR 2.5

Distances:
1 DIST = 2.47 cm
2 DIST = 3.10 cm

Cincinnati Children's
Intrauterine balloon retrieval
let the amniotic fluid (AF) wash the fetal lungs
Delivery at Term
Fetal tracheal occlusion for severe CDH

Retrieval of the balloon

Earlier than planned:
As late as possible
just prior to delivery
or at the time of earlier delivery

- **Ultrasound guided**
- **Fetoscopy**
  - Infuse a fluid pocket if necessary
- **Exit**
- **Tracheoscopy**
  - or percutaneous puncture
Fetoscopic Endoluminal Tracheal Occlusion: When to UN-PLUG?

- **26 W** → Fetoscopic balloon placement (PLUGING)
- **34 W** → Fetoscopic balloon retrieval (UN-PLUGING)
- **36 W** → Planned/ emergency delivery (PPROM) with EXIT strategy
- **After birth** → Neonatal surgery (defect repair)
Recommended Fetal Interventions and Surgeries

Supported by Level I Evidence

Myelomeningocele (MMC): Prenatal Open Repair
A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele

N. Scott Adzick, M.D., Elizabeth A. Thom, Ph.D., Catherine Y. Spong, M.D., John W. Brock III, M.D., Pamela K. Burrows, M.S., Mark P. Johnson, M.D., Lori J. Howell, R.N., M.S., Jody A. Farrell, R.N., M.S.N., Mary E. Dabrowiak, R.N., M.S.N., Leslie N. Sutton, M.D., Nalin Gupta, M.D., Ph.D., Noel B. Tulipan, M.D., Mary E. D’Alton, M.D., and Diana L. Farmer, M.D., for the MOMS Investigators*

CONCLUSIONS

Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT00060606.)
Goal of the Trial

To compare the safety and efficacy of in utero repair of open neural tube defects with that of the standard postnatal repair
Outcome variables

- Need for shunt
- Death by 1 year
- Neonatal and maternal morbidity
- Neurologic function (legs, bladder, bowel, neurodevelopmental)
- F/U at 12 & 30 months
Inclusion Criteria

• Myelomeningocele starting at T1-S1 with evidence of hindbrain herniation
• Singleton pregnancy 190 to 256 weeks, normal karyotype
• 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
- Kyphosis $\geq$ 30 degrees
- Maternal IDDM
- Isoimmunization
- Body mass index $\geq$ 35
- Other contraindications to elective surgery
MOMS TRIAL RESULTS

Significant decrease in shunt placement rate in perinatal surgery group: 40% v 82%

Significant increase in mobility in prenatal surgery group: 42% v 21%
LIMITATIONS

Uterine surgical incision induce uterine dynamics activation

Sometimes, a successful intervention is lost by preterm labor and subsequent preterm delivery.
FETENDO (FETal - ENDOscopy)
Fetoscopic Coverage of MMC

**ANTECEDENTS**

- J. Bruner / N. Tulipan
  - 1996

- Thomas Kohl
  - 2003

- D. Pedreira / R. Quintero
  - 2013
INNOVATION
Fetal Surgery for MMC

OPEN

FETOSCOPY

Sheep

Human
Percutaneous fetoscopic patch closure of human spina bifida aperta: advances in fetal surgical techniques may obviate the need for early postnatal neurosurgical intervention

Thomas Kohl · Kristina Tchatcheva · Waltraut Merz · Hans C. Wartenberg · Axel Heep · Andreas Müller · Axel Franz · Rüdiger Stressig · Winfried Willinek · Ulrich Gembruch
Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial

Denise A. L. Pedreira, MD, PhD; Nelci Zanon, MD, PhD; Koshiro Nishikuni, MD, PhD; Renato A. Moreira de Sá, MD, PhD; Gregório L. Acacio, MD, PhD; Ramen H. Chmaid, MD; Eftichia V. Kontopoulos, MD, PhD; Rubén A. Quintero, MD
Fetoscopic MMC Repair
We decided to close skin over the patch

STORZ
2 mm instruments
Fetoscopic MMC Repair
We decided to close skin over the patch

The V-Loc™
wound closure devices
Fetoscopic vs open MMC repair

- In a recent metaanalysis of 11 studies:
  - No difference in mortality or the rate of shunt placement for hydrocephalus.

- Percutaneous fetoscopic repair:
  - Higher rates of premature rupture of membranes (91 vs. 36%, \( p < 0.01 \))
  - Preterm birth (96 vs. 81%, \( p = 0.04 \))
  - Fetoscopic repair via maternal laparotomy reduced preterm birth.
  - The rate of dehiscence and leakage from the MMC repair site was higher after both
  - Lower rate of uterine dehiscence.

Kabgambe SK et al 2018
Fetoscopic vs open MMC repair

- Fetoscopic repair is a promising alternative to open fetal MMC repair
- Fetoscopic techniques should be optimized to overcome
In-utero Fetal Therapy

Principles

Treatments

Complications

Ethical Issues

Lecture Outline
Fetal Surgery Complications

A- Fetal Complications:

B- Maternal Complications:

C- Other Complications:
Fetal Surgery Complications

- **A- Fetal Complications:**
  - TTTS
  - FETO
  - Open NTD
  - Fetoscopic NTD
  - Shunt and RF
  - 31-32 wks
  - 34-35 wks
  - 36 wks
  - 34-35 wks

- **B- Maternal Complications:**
  - PPROM
  - Chorioamnionitis
  - Placenta Abruption

- **C- Other Complications:**
  - Pre-Term Delivery
  - 31-32 wks
  - 34-35 wks
  - 34-35 wks
  - 36 wks
  - 34-35 wks
Complications of open fetal surgery in MMC repair
1/3rd of women who underwent prenatal surgery had an area of dehiscence or a very thin pre-natal uterine scar at the time of delivery.
Complications of open fetal surgery in MMC repair

A- Fetal Complications:

- Hypoxemia with increased oxygen requirements
- Atelectasis
- Pulmonary edema and effusion
- Bronchopneumonia
- Ileus
- DVT/ PE

B- Maternal Complications:

C- Other Complications:

A- Fetal Complications:

B- Maternal Complications:

C- Other Complications:

Examples:

- Pseudoamniotic Band Syndrome
- Shunt Related Complications
- Fetal Bradycardia due to Maternal Hypothermia
  - Mirror Syndrome
Ethical Issues in Fetal Therapy

Fetal therapy must meet the following three criteria to be ethically permissible:

1- It should be a life-saving or should prevent or substantially mitigate serious or irreversible disease, injury, or handicap to the fetus or the child to be.

2- The proposed therapy should have a low mortality risk for the fetus and low or manageable risk of serious disease, injury, or handicap to the fetus or born child.

3- The maternal mortality and morbidity (disease or injury, or handicap) risk to the mother should be very low or manageable.
Ethical Issues in Fetal Therapy

- It is not recommended of any hospital, university or medical practice to allow an individual or team to perform ANY fetal surgery **without the appropriate training**, credentialing, facilities, support, and objective oversight.

- Criteria for a Center statement Upcoming
  - SMFM, ABOG, ACOG, APSA, APA, NAFTNET
THANKS FOR YOUR ATTENTION

Mounira.habli@cchmc.org
Acknowledgements

Fetal Care Center
Pediatric surgeon
MFM
Neonatologist
Cardiologist
Radiology
Nurses.
Pediatric specialities
Pre, Intra and Postoperative Complications with Fetoscopic Procedures and open Procedure.
Martinez et al. 2011 reported a retrospective study to assess the prevalence and clinical implications of inadvertent septostomy after laser therapy for TTTS.

Among 414 SFLP cases:
- 7.2% had septostomy occurred within the first week postoperatively.
- 1.9% cases diagnosed postnatally were complicated with Amniotic Band Syndrome, including limb constrictions.
- No limb amputations.
Frequency of adverse Perinatal Outcome
Pseudo Amniotic Band Syndrome

1.8% to 3.3% in Mono twin pregnancy after invasive procedure.

Winer et al. 2007 AJOG

Complications:

- Umbilical cord compression in a constrictive sheet
- Detachment of the ruptured amniotic membrane
- Fetal limb constrictions or amputations
- Facial cleft
- Intrauterine fetal death (IUFD) esp with umbilical cord is involved

Lafitte et al. 2017 AIUM
<table>
<thead>
<tr>
<th>Source</th>
<th>Case</th>
<th>Procedure</th>
<th>GA at Procedure, wk</th>
<th>Time of Detection</th>
<th>PPROM</th>
<th>GA at delivery, wk</th>
<th>Donor Outcome</th>
<th>Recipient Outcome</th>
<th>Affected Fetus</th>
<th>Affected Fetal Parts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winer et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1</td>
<td>FLP</td>
<td>21.0</td>
<td>2 prenatally</td>
<td>No</td>
<td>26.0</td>
<td>IUFD</td>
<td>LB</td>
<td>Rec</td>
<td>2 legs</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>FLP</td>
<td>23.0</td>
<td>diagnosed</td>
<td>No</td>
<td>34.0</td>
<td>IUFD</td>
<td>LB</td>
<td>Rec</td>
<td>Left arm</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>FLP</td>
<td>16.0</td>
<td>Yes</td>
<td></td>
<td>33.5</td>
<td>CC</td>
<td>LB</td>
<td>Rec</td>
<td>Right leg</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>FLP</td>
<td>21.0</td>
<td>Yes</td>
<td></td>
<td>30.0</td>
<td>IUFD</td>
<td>LB</td>
<td>Rec</td>
<td>Right leg</td>
</tr>
<tr>
<td></td>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FLP</td>
<td>19.0</td>
<td>Yes</td>
<td></td>
<td>25.5</td>
<td>IUFD</td>
<td>LB/LB</td>
<td>1 Rec</td>
<td>Right foot</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>FLP</td>
<td>19.0</td>
<td>No</td>
<td></td>
<td>33.0</td>
<td>CC</td>
<td>LB</td>
<td>Rec</td>
<td>Left arm</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>FLP</td>
<td>20.0</td>
<td>Yes</td>
<td></td>
<td>30.0</td>
<td>IUFD</td>
<td>LB</td>
<td>Rec</td>
<td>Left arm</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>FLP</td>
<td>16.0</td>
<td>Yes</td>
<td></td>
<td>31.0</td>
<td>IUFD/PABS (UC amputation)</td>
<td>LB</td>
<td>Rec</td>
<td>Right hand</td>
</tr>
<tr>
<td>Rujiwetpongstorn and Tongsong&lt;sup&gt;5&lt;/sup&gt;</td>
<td>9</td>
<td>S + A</td>
<td>24.0</td>
<td>PN</td>
<td>Yes</td>
<td>31.0</td>
<td>IUFD/PABS (UC amputation)</td>
<td>LB</td>
<td>Don</td>
<td>2 legs + 2 feet</td>
</tr>
<tr>
<td>Karunaratne et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>10</td>
<td>FLP</td>
<td>17.0</td>
<td>PN</td>
<td>NR</td>
<td>29.0</td>
<td>LB</td>
<td>LB</td>
<td>Rec</td>
<td>2 feet</td>
</tr>
<tr>
<td>Rodrigues et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>11</td>
<td>FLP</td>
<td>16.4</td>
<td>PN</td>
<td>No</td>
<td>39.7</td>
<td>IUFD</td>
<td>Don</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shamshirsaz et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>FLP</td>
<td>16.6</td>
<td>PN</td>
<td>No</td>
<td>33.1</td>
<td>LB/LB</td>
<td>LB</td>
<td>Rec</td>
<td>Left foot</td>
</tr>
<tr>
<td>Ting et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>13</td>
<td>FLP</td>
<td>18.9</td>
<td>25.1</td>
<td>No</td>
<td>29.3</td>
<td>IUFD</td>
<td>LB</td>
<td>Rec</td>
<td>Right arm + left leg</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>BCC</td>
<td>16.1</td>
<td>20.3</td>
<td>No</td>
<td>22.1</td>
<td>CC</td>
<td>TOP</td>
<td>Rec</td>
<td>Right arm + UC</td>
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<tr>
<td>Our case 1</td>
<td>15</td>
<td>FLP</td>
<td>18.3</td>
<td>PN</td>
<td>No</td>
<td>26.1</td>
<td>IUFD</td>
<td>IUFD/UC</td>
<td>Rec</td>
<td>Left hand</td>
</tr>
<tr>
<td>Our case 2</td>
<td>16</td>
<td>FLP</td>
<td>21.1</td>
<td>PN</td>
<td>Yes</td>
<td>27.6</td>
<td>IUFD/PABS</td>
<td>Rec</td>
<td></td>
<td>Face + UC</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>FLP</td>
<td>16.1</td>
<td>PN</td>
<td>No</td>
<td>30.7</td>
<td>IUFD/PABS</td>
<td>Rec</td>
<td></td>
<td>Right hand + UC</td>
</tr>
<tr>
<td><strong>Summary, n (%)</strong></td>
<td></td>
<td>FLP, 15/17 (88)</td>
<td>Mean, 18.8</td>
<td>AN, 4/17 (23)</td>
<td>PPROM, 7/16 (44)</td>
<td>Mean, 30.1</td>
<td>IUFD, 9/16 (56)</td>
<td>LB, 13/18 (72)</td>
<td>Rec, 15/17 (88)</td>
<td><strong>Limbs, 17/17 (100)</strong></td>
</tr>
</tbody>
</table>
Fetal Vascular Limb Occlusion

- 0.02% is incidence in general population

- Reported incidence
  - 0.52% (4/755) monochorionic twins
  - 0.51% (2/391) for those cases complicated by TTTS

- Suggested pathologic mechanisms:
  - Polycythemia-hyperviscosity syndrome
  - Elevated angiotensin level
  - Release of thrombi after co-twin death
  - Umbilical arterial-steal syndrome
  - Vascular injury
  - Laser induced thrombi
  - Hypertension

Lopriore 2008 Pre Diagnosis
Rijnders 2000 Prosth Ortho
### Pregnancy Outcome and Vascular Limb Constriction S/p SFLP

<table>
<thead>
<tr>
<th>Gestational age at diagnosis</th>
<th>stage</th>
<th>Affected Twin</th>
<th>Affected Limb</th>
<th>Side</th>
<th>Therapy</th>
<th>Time of DX</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.8±2.41</td>
<td>2(I)</td>
<td>95% RT</td>
<td>85% lower</td>
<td>71% right</td>
<td>7(Laser)</td>
<td>6 feto</td>
<td>5 IUFD</td>
</tr>
<tr>
<td>16-26 weeks</td>
<td>6(III)</td>
<td>5% Do</td>
<td>15% Upper</td>
<td>29% left</td>
<td>7( AR only)</td>
<td>2 US</td>
<td>Postnatally</td>
</tr>
</tbody>
</table>

Schrey 2012 AJOG
Twin anemia-polycythemia sequence (TAPS)

- 2007 first case published
- TAPS is characterized by large intertwin hemoglobin (Hb) differences without signs of TTTS.
- Spontaneous in 3–5% of monochorionic twin pregnancies
- 2-13% after laser surgery for TTTS

Pathogenesis:
- Few arteriovenous vascular anastomoses
- 11% incidence of AA anastomoses vs. 25-80% in TTTS

Robyr 2006 AJOG
Lopriore 2007 placenta
Lewi 2008 AJOG
Lopriore 2009 AJOG
Habli 2009 AJOG
Twin anemia-polycythemia sequence (TAPS)

Diagnosis:
- Absence of oligohydramnios and polyhydramnios on antenatal ultrasound.

<table>
<thead>
<tr>
<th>Antenatal criteria</th>
<th>Postnatal criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-PSV &gt;1.5 MoM in the donor and MCA-PSV &lt;1.0 MoM in the recipient</td>
<td>Intertwin Hb difference &gt;8.0 g/dl and at least one of the following:</td>
</tr>
<tr>
<td></td>
<td>- Reticulocyte count ratio &gt;1.7</td>
</tr>
<tr>
<td></td>
<td>- Placenta with only small (diameter &lt;1 mm) vascular anastomoses</td>
</tr>
</tbody>
</table>

- Doppler ultrasound on a regular basis (at least once every 2 weeks) in all monochorionic twins
### Twin anemia-polycythemia sequence (TAPS) Classifications

<table>
<thead>
<tr>
<th>Antenatal stage</th>
<th>Findings at Doppler ultrasound examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>MCA-PSV donor &gt;1.5 MoM and MCA-PSV recipient &lt;1.0 MoM, without other signs of fetal compromise</td>
</tr>
<tr>
<td>Stage 2</td>
<td>MCA-PSV donor &gt;1.7 MoM and MCA-PSV recipient &lt;0.8 MoM, without other signs of fetal compromise</td>
</tr>
<tr>
<td>Stage 3</td>
<td>as stage 1 or 2, with cardiac compromise of donor, defined as critically abnormal flow&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage 4</td>
<td>hydrops of donor</td>
</tr>
<tr>
<td>Stage 5</td>
<td>intrauterine demise of one or both fetuses preceded by TAPS</td>
</tr>
</tbody>
</table>

<sup>a</sup> Critically abnormal Doppler is defined as absent or reversed end-diastolic flow in umbilical artery, pulsatile flow in the umbilical vein, increased pulsatility index or reversed flow in ductus venosus.
Management Of TAPS

- Expectant management
- Induction of labor,
- Intrauterine blood transfusion
  - Short duration
  - Intraperitoneal > IV due to slow absorption
- Selective feticide
- Repeat fetoscopic laser surgery
  - Solomon technique vs Selective Laser surgery
Recurrent TTTS

- TTTS recurrence rate
  - Prospective studies ranged from 0 to 16%
  - Retrospective studies ranged from 1 to 6%

- Pathology:
  - residual large anastomoses mainly AA vs TAPS is small AV

- Total reported cases among studies 26 case of known outcome
  - Overall fetal survival was 58% (30/52)
  - Neurologically intact survival 44%(23/52)

- Among liveborn twins, the incidence of death or neurologically impaired survival was 23.3%.

WALSH 2012 UOG
Lopriore 2009 AJOG
Lewi 2006 AJOG
Management of Recurrent TTTS

<table>
<thead>
<tr>
<th>Management strategy</th>
<th>Frequency (n (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat SFLP</td>
<td>32 (29.6)</td>
</tr>
<tr>
<td>Expectant management/delivery</td>
<td>21 (19.4)</td>
</tr>
<tr>
<td>Amnioreduction</td>
<td>15 (13.9)</td>
</tr>
<tr>
<td>Cord occlusion</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Data not available</td>
<td>37 (34.3)</td>
</tr>
<tr>
<td>TTTS</td>
<td>TAPS</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Transfusion through small anastomoses</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>Spontaneous TAPS: 1–5%</td>
</tr>
<tr>
<td><strong>Prenatal diagnosis</strong></td>
<td>Post-laser TAPS: up to 16%</td>
</tr>
<tr>
<td><strong>Oligo-polyhydramnios on prenatal US</strong></td>
<td>Abnormal US Dopplers: MCA-PSV ≥1.5 MoM in donor &amp; ≤1.0 MoM in recipient, without twin oligo-polyhydramnios sequence</td>
</tr>
<tr>
<td><strong>Postnatal diagnosis</strong></td>
<td>Intertwin Hb difference ≥8 g/dL</td>
</tr>
<tr>
<td><strong>Antenatal staging</strong></td>
<td>AND at least one of the following:</td>
</tr>
<tr>
<td><strong>Stage 1:</strong></td>
<td>Reticulocyte count ratio &gt;1.7</td>
</tr>
<tr>
<td>Donor DVP &lt; 2 cm,</td>
<td>Small AV-anastomoses (diameter &lt; 1 mm)</td>
</tr>
<tr>
<td>recipient DVP &gt; 8 cm,</td>
<td></td>
</tr>
<tr>
<td>DVP &gt; 10 cm (≥20 weeks)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 2:</strong></td>
<td></td>
</tr>
<tr>
<td>Donor: no bladderfilling,</td>
<td></td>
</tr>
<tr>
<td>recipient: full bladder</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 3:</strong></td>
<td></td>
</tr>
<tr>
<td>Doppler abnormalities</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 4:</strong></td>
<td></td>
</tr>
<tr>
<td>Hydrops</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 5:</strong></td>
<td></td>
</tr>
<tr>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 2:</strong></td>
<td></td>
</tr>
<tr>
<td>MCA-PSV ≥1.5 MoM &amp; ≤1.0 MoM</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 3:</strong></td>
<td></td>
</tr>
<tr>
<td>Doppler abnormalities</td>
<td></td>
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<tr>
<td><strong>Stage 4:</strong></td>
<td></td>
</tr>
<tr>
<td>Hydrops</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 5:</strong></td>
<td></td>
</tr>
<tr>
<td>IUFD</td>
<td></td>
</tr>
</tbody>
</table>
PPROM, PTD and Fetoscopic Surgery
PPROM and TTTS

- Incidence of iPPROM, vary significantly
  - 8% of diagnostic fetoscopies
  - 30% of operative fetoscopy procedure

- Potential sequelae of PPROM
  - oligohydramnios-related pulmonary hypoplasia
  - Chorioamnionitis
  - Preterm delivery

- Little is known about the Patho-mechanisms

- Potential influencing factors
  - Diameter of the surgical instrument
  - Number of entries to the uterine cavity
# iPPROM and Placental Laser Ablation in TTTS

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Ø, mm</th>
<th>GA (Tx)</th>
<th>iPPROM, %</th>
<th>GA (iPPROM)</th>
<th>GA (birth)</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Lia, 1995 [32]</td>
<td>26</td>
<td>3.9</td>
<td>21 (18–24)</td>
<td>53 (≤36 weeks)</td>
<td>not known</td>
<td>27 (19–37)</td>
<td>53 (c)</td>
</tr>
<tr>
<td>Deprest, 1998 [38]</td>
<td>6</td>
<td>4</td>
<td>21 (19–22)</td>
<td>50</td>
<td>29 (24–34)</td>
<td>31 (24–36)</td>
<td>67 (c)</td>
</tr>
<tr>
<td>Habli, 2009 [14]</td>
<td>152</td>
<td>3.3</td>
<td>21 ± 3</td>
<td>26</td>
<td>26</td>
<td>31 ± 5</td>
<td>78 (f)</td>
</tr>
<tr>
<td>Middeldorp, 2007 [34]</td>
<td>10</td>
<td>3.3</td>
<td>27 (26–28)*</td>
<td>0 (&lt;2 weeks)</td>
<td>–</td>
<td>31 (28–37)*</td>
<td>100 (n)</td>
</tr>
<tr>
<td>Middeldorp, 2007 [39]</td>
<td>100</td>
<td>3.3</td>
<td>20 (16–26)*</td>
<td>13 (&lt;2 weeks)</td>
<td>not known</td>
<td>33 (18–40)*</td>
<td>70 (n)</td>
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<tr>
<td>Peiro, 2009 [40]</td>
<td>148</td>
<td>3</td>
<td>21 (15–25)</td>
<td>12</td>
<td>not known</td>
<td>35</td>
<td>86 (p)</td>
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<tr>
<td>Quintero, 2001 [41]</td>
<td>72</td>
<td>3 (1–2)</td>
<td>21 (17–26)</td>
<td>6 (≤3 weeks)</td>
<td>not known</td>
<td>32 (19–41)</td>
<td>48</td>
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<td>Ruano, 2009 [33]</td>
<td>19</td>
<td>2.2</td>
<td>22 (19–26)</td>
<td>11</td>
<td>29 (26–32)</td>
<td>33 (26–38)</td>
<td>53</td>
</tr>
<tr>
<td>Said, 2008 [42]</td>
<td>10</td>
<td>2.8</td>
<td>20 (18–24)*</td>
<td>30</td>
<td>2 × &lt;22 weeks, 1 × 29 weeks</td>
<td>30 (22–37)*</td>
<td>65 (c)</td>
</tr>
<tr>
<td>Sepulveda, 2007 [43]</td>
<td>33</td>
<td>3.8</td>
<td>21 (17–25)*</td>
<td>15 (viable)</td>
<td>not known</td>
<td>32 (23–38)</td>
<td>52 (p)</td>
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<tr>
<td>Ville, 1998 [37]</td>
<td>132</td>
<td>3.3</td>
<td>21 (15–27)*</td>
<td>10 (oligo)</td>
<td>not known</td>
<td>32 (18–40)</td>
<td>55 (c)</td>
</tr>
<tr>
<td>Winer, 2008 [13]</td>
<td>438</td>
<td>3.3</td>
<td>21 (15–26)</td>
<td>30</td>
<td>14% ≤3 weeks post Tx</td>
<td>30 ± 6</td>
<td>not known</td>
</tr>
</tbody>
</table>

**Total**: 1146

Max Dia 3.3(2.2-4)

Mean GA at TX 21 (15-28) wks

27% (11-50%)

GA at PPROM 28(24-29) weeks

Mean GA at del 31(18-41) wks

66% (44-100%)
Maximum diameter of the instrument significantly predicted the iPPROM rate.

iPPROM rate significantly linked to gestational age at birth and fetal survival.
### Preterm Delivery and Fetoscopic Procedure

<table>
<thead>
<tr>
<th>Author/year</th>
<th>TTTS Pregnancy (n)</th>
<th>GA at delivery (wks)</th>
<th>Mode delivery</th>
<th>PTL &lt;33wks (%)</th>
<th>ARF (%)</th>
<th>NEC (%)</th>
<th>RDS (%)</th>
<th>IVH 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickson-2000</td>
<td>112</td>
<td>29</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>3</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Duncomb-2003</td>
<td>69</td>
<td>29.4</td>
<td></td>
<td></td>
<td>4.8</td>
<td>2.9</td>
<td>62</td>
<td>5.8</td>
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<td>Lepoir-2005</td>
<td>85</td>
<td>32.6</td>
<td>34</td>
<td>66</td>
<td>3</td>
<td>34</td>
<td>14</td>
<td></td>
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<tr>
<td>Lufti-2005</td>
<td>48</td>
<td>27</td>
<td>73</td>
<td>27</td>
<td>5.2</td>
<td></td>
<td>27</td>
<td>13</td>
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<td>Robyr-2006</td>
<td>101</td>
<td>31</td>
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<td></td>
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<tr>
<td>Acosta-2007</td>
<td>101</td>
<td>33</td>
<td>44</td>
<td>NA</td>
<td>4.3</td>
<td>43</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lenclen-2007</td>
<td>79</td>
<td>29</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 13-17% rate of PTD before 24 weeks
- 22-29% rate of PTD before 28 weeks
- 49-54% rate of PTD before 34 weeks
Incidence and Pregnancy Outcome Chorio-amnio Separation (CAS) in Fetal Endoscopic Cases

Incidence
- 5-19% in SFLP for TTTS
- Up to 21% Spontaneous
- 4-10% Amniocentesis

Risk Factors for CAS:
- Preoperative Recipient DVP is between 8-12
- Higher rate of iatrogenic septostomy

Pregnancy outcome
- 15% Pregnancy loss <24 weeks
- 40% delivered <37 week
- 28% IUFD
- 21% rate of amniotic Band syndrome mostly around the cord
- 4% rate of neonatal death

Habli 2009 AJOG
Papanna 2010 AJOG
Graf 2002 JP
### Pregnancy Outcome Chorio-amnion Separation (CAS) in TTTS treated with SFLP

<table>
<thead>
<tr>
<th></th>
<th>CAS (n=19)</th>
<th>No CAS (n=78)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>PPROM</td>
<td>14 (74)</td>
<td>18 (23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age at PPROM (wk)</td>
<td>24.6±3.5</td>
<td>27.5±4.2</td>
<td>.06</td>
</tr>
<tr>
<td>Procedure to PPROM (d)</td>
<td>30.2±23.7</td>
<td>49.3±29.7</td>
<td>.1</td>
</tr>
<tr>
<td>Gestational age at delivery (wk)</td>
<td>28±3.9</td>
<td>31.4±3.9</td>
<td>.001</td>
</tr>
<tr>
<td>Procedure to delivery (d)</td>
<td>51.6±28.2</td>
<td>71.3±29.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Survival to birth</td>
<td>27/38 (71.1)</td>
<td>136/156 (87)</td>
<td>.03</td>
</tr>
<tr>
<td>Neonatal survival</td>
<td>24/38 (63.2)</td>
<td>131/156 (84)</td>
<td>.016</td>
</tr>
<tr>
<td>At least one survival to neonatal period</td>
<td>14 (74)</td>
<td>73 (94)</td>
<td>.03</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient</td>
<td>1,187.8±398.8</td>
<td>1,663.6±610.7</td>
<td>.02</td>
</tr>
<tr>
<td>Donor</td>
<td>1,082.8±314.4</td>
<td>1,444.1±693.8</td>
<td>.02</td>
</tr>
</tbody>
</table>

Papanna 2010 AJOG
Complication in Open Fetal Procedures
Acute Intraoperative Complications During EXIT

Maternal

- Maternal haemorrhage.
  - Uterine Relaxation
  - Post-EXIT uterine atony
- Blood Loss
  - Average blood loss of 848(±574) ml
  - Massive bleeding (2.5 l) from the placental edge
- No maternal deaths
- Hypotension is a side effect of maternal position and tocolysis.

FETAL

- Fetal bradycardia and acidosis.
- Increase fetal acidosis
- Procedure times (up to 60 minutes) with no evidence of cardiovascular depression or acidosis

Michaliska 1997 JPS
Gaiser RR 199 An analg
Bouchard 2002 JPS
Pulmonary Edema during Fetal Surgery

Etiology:

- Fluid over load preoperatively
- Tocolytic during or post procedure.
- Tracking of amniotic fluid and saline irrigating fluid along a trocar into a venous channel in the myometrium.
- Uterine manipulation releases prostaglandins and thromboplastins into the maternal circulation and may result in increased pulmonary endothelial

Resolved average 1.9 days

Prevention:

- Fluid restriction during surgery
- No multiple tocolytics.

Robinson 2008 An analg
Difedrico 1998 AJOG
# Open Fetal Surgery (MOMS) Maternal Complications

<table>
<thead>
<tr>
<th></th>
<th>UCSF</th>
<th>MOMS2011</th>
<th>Vanderbilt 2014</th>
<th>CHOP2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of procedures</td>
<td>79</td>
<td>91</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>Pulmonary edema (n, %)</td>
<td>22 (28)</td>
<td>5 (6)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Placental abruption (n, %)</td>
<td>7 (9)</td>
<td>6 (7)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Chorioamnionitis (n, %)</td>
<td>7 (9)</td>
<td>2 (3)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Immediate transfusion (n, %)</td>
<td>11 (13)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Transfusion at delivery (n, %)</td>
<td>8 (9)</td>
<td>0</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Dehiscence scar at delivery (n, %)</td>
<td>10 (11)</td>
<td>3 (7)</td>
<td>7 (8)</td>
<td></td>
</tr>
<tr>
<td>Very thin scar at delivery (n, %)</td>
<td>21 (24)</td>
<td>2 (4)</td>
<td>36 (41)</td>
<td></td>
</tr>
</tbody>
</table>
### Post MOMS Trial Reported Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHOP post MOMS (N = 100)</th>
<th>MOMS (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age at evaluation (weeks)</strong></td>
<td>21.6 ± 1.6</td>
<td>23.6 ± 1.4</td>
</tr>
<tr>
<td><strong>Lesion level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T11/T12</td>
<td>6 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>L1/L2</td>
<td>21 (21%)</td>
<td>21 (27%)</td>
</tr>
<tr>
<td>L3/L4</td>
<td>66 (66%)</td>
<td>30 (38%)</td>
</tr>
<tr>
<td>L5/S1</td>
<td>7 (7%)</td>
<td>23 (29%)</td>
</tr>
<tr>
<td><strong>Gestational age at fetal surgery (weeks)</strong></td>
<td>23.3</td>
<td>24.2</td>
</tr>
<tr>
<td><strong>Maternal blood transfusion at fetal surgery</strong></td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Fetal resuscitation</strong></td>
<td>5 (5%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td><strong>Total operative time (min)</strong></td>
<td>78.5 ± 11.9</td>
<td>105 ± 23.2</td>
</tr>
<tr>
<td><strong>Pulmonary edema</strong></td>
<td>2 (2%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td><strong>Chorioamniotic membrane separation</strong></td>
<td>22 (23%)</td>
<td>20 (26%)</td>
</tr>
<tr>
<td><strong>PPROM</strong></td>
<td>31 (32%)</td>
<td>36 (46%)</td>
</tr>
<tr>
<td><strong>Preterm labor</strong></td>
<td>36 (37%)</td>
<td>30 (38%)</td>
</tr>
<tr>
<td><strong>Oligohydramnios</strong></td>
<td>8 (8%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td><strong>Average gestational age at delivery (weeks)</strong></td>
<td>34.3</td>
<td>34.1</td>
</tr>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>9 (9%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>30–34</td>
<td>35 (36%)</td>
<td>26 (33%)</td>
</tr>
<tr>
<td>35–36</td>
<td>26 (27%)</td>
<td>26 (33%)</td>
</tr>
<tr>
<td>&gt;37</td>
<td>26 (27%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td><strong>Birthweight (g)</strong></td>
<td>2416 ± 722</td>
<td>2383 ± 688</td>
</tr>
<tr>
<td><strong>Perinatal death</strong></td>
<td>6 (6%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td><strong>Maternal transfusion at delivery</strong></td>
<td>3 (3%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td><strong>Hysterotomy at delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>44/87 (51%)</td>
<td>49/76 (64%)</td>
</tr>
<tr>
<td>Thin</td>
<td>36/87 (41%)</td>
<td>19/76 (25%)</td>
</tr>
<tr>
<td>Focal dehiscence</td>
<td>6/87 (7%)</td>
<td>7/76 (9%)</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>1/87 (1%)</td>
<td>1/76 (1%)</td>
</tr>
</tbody>
</table>
Chorioamniotic membrane separation and preterm premature rupture of membranes complicating in utero myelomeningocele repair

Shelly Soni, MD; Julie S. Moldenhauer, MD; Susan S. Spinner, MSN, RN; Norma Rendon, MS; Nahla Khalek, MD, MPH; Juan Martinez-Poyer, MD; Mark P. Johnson, MD, MS; N. Scott Adzick, MD, MMM

- a retrospective review of 88 patients undergoing prenatal MMC repair and subsequent delivery from January 2011 through December 2013 at 1 institution.

- 23.9% with chorioamniotic membrane separation (CAS) by ultrasound
  - 47.4% global CAS
  - 52.4% Local CAS
- 30.7% rate of PPROM.
- interval from fMMC repair to PPROM was 47 days.
## Perioperative Factors and CAS Risk

### Perioperative factors in chorioamniotic membrane separation vs no chorioamniotic membrane separation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Chorioamniotic membrane separation, N = 21</th>
<th>No membrane separation, N = 67</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>30.7 ± 3.6</td>
<td>29.2 ± 4.8</td>
<td>.2</td>
</tr>
<tr>
<td>Parity [nulliparous], N (%)</td>
<td>5 (23.8)</td>
<td>28 (41.8)</td>
<td>.13</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>28.0 ± 4.4</td>
<td>26.1 ± 4.2</td>
<td>.07</td>
</tr>
<tr>
<td>Intraoperative version done, N (%)</td>
<td>5 (22.7)</td>
<td>30 (45.4)</td>
<td>.44</td>
</tr>
<tr>
<td>Placental location, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior placenta</td>
<td>6 (28.6)</td>
<td>36 (53.7)</td>
<td></td>
</tr>
<tr>
<td>Posterior placenta</td>
<td>15 (68.2)</td>
<td>31 (47.0)</td>
<td>.05</td>
</tr>
<tr>
<td>Gestational age at fMMC repair, wk, mean ± SD</td>
<td>22.5 ± 1.6</td>
<td>23.4 ± 1.3</td>
<td>.01</td>
</tr>
<tr>
<td>Total operative time, min, mean ± SD</td>
<td>77.9 ± 13.3</td>
<td>79.5 ± 11.6</td>
<td>.6</td>
</tr>
<tr>
<td>Hysterotomy time, min, mean ± SD</td>
<td>38.4 ± 7.8</td>
<td>36.9 ± 10.2</td>
<td>.6</td>
</tr>
<tr>
<td>LOS, post-fMMC repair, d, mean ± SD</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 1.0</td>
<td>.65</td>
</tr>
</tbody>
</table>
### Pregnancy outcomes with chorioamniotic membrane separation vs no chorioamniotic membrane separation

<table>
<thead>
<tr>
<th></th>
<th>Chorioamniotic membrane separation, N = 21</th>
<th>No membrane separation, N = 67</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPROM, N (%)</td>
<td>13 (59.1)</td>
<td>14 (21.2)</td>
<td>.008</td>
</tr>
<tr>
<td>Preterm labor, N (%)</td>
<td>6 (28.6)</td>
<td>23 (34.3)</td>
<td>.79</td>
</tr>
<tr>
<td>Gestational age at delivery, wk, mean ± SD</td>
<td>32.1 ± 4.2</td>
<td>34.4 ± 3.5</td>
<td>.01</td>
</tr>
<tr>
<td>Period from fMMC repair to delivery, d, mean ± SD</td>
<td>65.7 ± 28.7</td>
<td>75.9 ± 24.2</td>
<td>.11</td>
</tr>
</tbody>
</table>

fMMC, fetal myelomeningocele; PPROM, preterm premature rupture of membranes.

## Outcomes for global vs local chorioamniotic membrane separation

<table>
<thead>
<tr>
<th></th>
<th>Global CMS, N = 9</th>
<th>Local CMS, N = 12</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at fMMC repair, wk, mean ± SD</td>
<td>22.9 ± 1.6</td>
<td>22.8 ± 1.8</td>
<td>.9</td>
</tr>
<tr>
<td>fMMC repair total operative time, min, mean ± SD</td>
<td>82.1 ± 13.3</td>
<td>74.2 ± 12.8</td>
<td>.2</td>
</tr>
<tr>
<td>PPROM, N (%)</td>
<td>5 (55.6)</td>
<td>8 (66.7)</td>
<td>.7</td>
</tr>
<tr>
<td>Preterm delivery, N (%)</td>
<td>1 (11.1)</td>
<td>5 (41.7)</td>
<td>.18</td>
</tr>
<tr>
<td>Gestational age at delivery, wk, mean ± SD</td>
<td>31.6 ± 4.8</td>
<td>32.9 ± 2.4</td>
<td>.4</td>
</tr>
</tbody>
</table>
Perioperative factors in preterm premature rupture of membranes

<table>
<thead>
<tr>
<th></th>
<th>No PPROM, N = 61</th>
<th>PPROM, N = 27</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>29.6 ± 4.6</td>
<td>29.4 ± 4.7</td>
<td>.86</td>
</tr>
<tr>
<td>Parity [nulliparous], N (%)</td>
<td>18 (29.5)</td>
<td>15 (55.6)</td>
<td>.03</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>26.1 ± 4.4</td>
<td>27.5 ± 4.0</td>
<td>.15</td>
</tr>
<tr>
<td>Intraoperative version, N (%)</td>
<td>28 (45.9)</td>
<td>6 (22.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Anterior placenta, N (%)</td>
<td>30 (49.2)</td>
<td>12 (44.4)</td>
<td>.82</td>
</tr>
<tr>
<td>Posterior placenta, N (%)</td>
<td>31 (50.8)</td>
<td>15 (55.6)</td>
<td>.82</td>
</tr>
<tr>
<td>Gestational age at fMMC repair, wk, mean ± SD</td>
<td>23.7 ± 1.2</td>
<td>22.5 ± 1.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total operative time, min, mean ± SD</td>
<td>78.4 ± 12.2</td>
<td>80.8 ± 11.3</td>
<td>.4</td>
</tr>
<tr>
<td>Hysterotomy time, min, mean ± SD</td>
<td>36.9 ± 10.4</td>
<td>38.1 ± 7.8</td>
<td>.62</td>
</tr>
<tr>
<td>Fetal operative time, min, mean ± SD</td>
<td>17.9 ± 5.4</td>
<td>19.7 ± 5.2</td>
<td>.1</td>
</tr>
<tr>
<td>Maternal LOS post-fMMC repair, d, mean ± SD</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 1.0</td>
<td>.65</td>
</tr>
<tr>
<td>Membrane separation, N (%)</td>
<td>8 (13.1)</td>
<td>13 (18.5)</td>
<td>.008</td>
</tr>
<tr>
<td>Global CMS, N (%)</td>
<td>4 (6.5)</td>
<td>5 (18.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Local CMS, N (%)</td>
<td>4 (6.5)</td>
<td>8 (29.6)</td>
<td>.006</td>
</tr>
</tbody>
</table>
Pregnancy Outcome in Pregnancies complicated with CAS

<table>
<thead>
<tr>
<th></th>
<th>No PPROM</th>
<th>PPROM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm labor, N (%)</td>
<td>17 (27.9)</td>
<td>12 (44.4)</td>
<td>.1</td>
</tr>
<tr>
<td>Gestational age at delivery, wk, mean ± SD</td>
<td>34.9 ± 3.5</td>
<td>31.6 ± 3.4</td>
<td>.0001</td>
</tr>
<tr>
<td>Birthweight, g, mean ± SD</td>
<td>2676.1 ± 652.9</td>
<td>1852.3 ± 535.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Perinatal loss, N (%)</td>
<td>3/61 (4.9)</td>
<td>2/27 (7.4)</td>
<td>.64</td>
</tr>
</tbody>
</table>

PPROM, preterm premature rupture of membranes.

Wilson et 2010 reported subsequent pregnancy outcome through a survey of 47 patients managed at CHOP and had open fetal surgery.

- 59% had one sub pregnancy
- 41% had more than one sub pregnancy
### Antepartum Outcome In Subsequent Pregnancies after open fetal surgery

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage: spontaneous</td>
<td>9</td>
</tr>
<tr>
<td>Miscarriage: surgical</td>
<td>2 (unintended)</td>
</tr>
<tr>
<td>Delivery &gt;20 wk</td>
<td>36 pregnancies (35 singleton; 1 twin pair)</td>
</tr>
<tr>
<td>Uncomplicated, &gt;20 wk, n (%)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>Complicated, &gt;20 wk, n (%)</td>
<td>16 (44)</td>
</tr>
<tr>
<td>Excessive bleeding/APH, n (%)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>PROM, n (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>PTL, n (%)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>PTD, n (%)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Placental factors, n (%)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>PIH, n (%)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>GDM, n (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Excessive bleeding at delivery, n (%)</td>
<td>2 (6), 1 transfusion/C hyst</td>
</tr>
<tr>
<td>Rupture (5)/dehiscence (5), n (%)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Prolonged hospital stay, n (%)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>
# Neonatal Outcome In Subsequent Pregnancies after open fetal surgery

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton</td>
<td>35</td>
</tr>
<tr>
<td>Twin pair</td>
<td>2</td>
</tr>
<tr>
<td>Average gestational age</td>
<td>36 wk</td>
</tr>
<tr>
<td>Average birthweight</td>
<td>2.99 kg</td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>26</td>
</tr>
<tr>
<td>Complicated</td>
<td>11 (twin pair counted twice)</td>
</tr>
<tr>
<td>Prematurity (respiratory)</td>
<td>10</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>5</td>
</tr>
<tr>
<td>Brain/CNS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (CNS i IVH)</td>
</tr>
<tr>
<td>Lung&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (24 wk prematurity)</td>
</tr>
<tr>
<td>Heart</td>
<td>1 (VSD)</td>
</tr>
<tr>
<td>Skin</td>
<td>2 (port wine lesion/congenital nevi; aplasia cutis congenital)</td>
</tr>
<tr>
<td>Condition</td>
<td>Score Range</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
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</tr>
<tr>
<td>Syndrome</td>
<td></td>
</tr>
<tr>
<td>Liver position</td>
<td></td>
</tr>
<tr>
<td>LV/RV disproportion</td>
<td></td>
</tr>
<tr>
<td>Sac or no Sac</td>
<td></td>
</tr>
<tr>
<td>LHR</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>60% survival</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>100% survival</td>
</tr>
<tr>
<td>PPLV</td>
<td></td>
</tr>
<tr>
<td>&lt; 15%</td>
<td>High risk</td>
</tr>
<tr>
<td>&gt; 22%</td>
<td>Low risk</td>
</tr>
<tr>
<td>TLV late 32-34 weeks</td>
<td></td>
</tr>
<tr>
<td>&gt; 25cc</td>
<td>Favorable</td>
</tr>
<tr>
<td>&lt; 18cc</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Modified Magoon Index</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.8</td>
<td>Severe pulm htn</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>Mild pulm htn</td>
</tr>
</tbody>
</table>

**CDH Prognostic Profile**
CDH Evaluation

- Comprehensive Ultrasound at time of diagnosis
  - Follow up Q 2 weeks for growth scan
  - Antenatal testing.
  - Reevaluation to assess severity again at 32-34 weeks

- Fetal echo at time of evaluation

- Fetal MRI at time of evaluation and repeated at 32-34 weeks.
  - Present predicted lung volume
  - Total lung volumes.
Differential Effect of Nifedipine on Donor and Recipient Survival

Recipient Survival

- Nifedipine: 89% (125/141)
- Control: 78% (119/152)

p < 0.018
Conclusions

- Numerous prenatal prognostic indicators in CDH
- Predict pulmonary hypoplasia and pulmonary hypertension
- Institution specific outcomes
- CDH-CPI may adjust for conflicting indicators
Principles of Fetal Surgery

- Correct and precise prenatal diagnosis
- Absence of associated anomaly
- Knowledge of the natural history
- High perinatal morbidity/mortality
- Absence of effective neonatal therapy
- Animal studies showing favorable results
- Performed in specialized centers - multidisciplinary approach
- Not compromise the reproductive future
- Should not increase maternal mortality