“The history of man for the nine months preceding his birth would, probably, be far more interesting and contain events of greater moment than all the three score and ten years that follow it.”

Samuel Taylor Coleridge
Miscellanies Aesthetic and Literary, 1803
Twin Anemia Polycythemia Sequence

- A true form of feto-fetotransfusion
- Characterized by large intertwin hemoglobin differences without signs of twin oli/poly sequence
- Occurs spontaneously in 3 to 5% of monochorionic diamniotic twins
- Chronic transfusion via < 1 mm placental vessel
- Occurs in 0.3 to 13% of cases after fetoscopic laser
Twin Anemia Polycythemia Sequence

- Doppler ultrasound abnormalities showing an increased
- Increased peak systolic velocity in the MCA of donor twin
- Consistent with anemia
- Decreased MCA-PSV in the recipient twin
- Suggestive of polycythemia

Twin Anemia Polycythemia Sequence

Antenatal Findings at Doppler Ultrasound Examination

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</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*</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>

* 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.
## Twin Anemia Polycythemia Sequence

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>75%</td>
</tr>
<tr>
<td>Intra-uterine transfusion</td>
<td>100%</td>
</tr>
<tr>
<td>Fetoscopic laser</td>
<td>100%</td>
</tr>
<tr>
<td>IUT and Fetoscopic Laser</td>
<td>100%</td>
</tr>
<tr>
<td>Selective fetocide</td>
<td>50%</td>
</tr>
<tr>
<td>Termination of pregnancy</td>
<td>0%</td>
</tr>
</tbody>
</table>

TWIN-TWIN TRANSFUSION SYNDROME

Unsolved problem

- Most common complication in MC twins
- 4-35% of all MC gestations in US
- 0.1-0.9 per 1000 births
- 17% of all perinatal mortality in twins
- Mortality of 80-100% if untreated
- Mortality of 15-63% even with treatment
Twin-Twin Transfusion Syndrome

Diagnostic Criteria

- Neonatal criteria
  - Discordant cord blood Hgb > 5 g/dl
  - Discordant birth weight > 20%
- Non-TTTS meeting criteria
  - 19/130 had Hgb > 5 g/dl
  - Growth restriction without TTTS
  - Fetal acidosis, hypoxemia
  - Polycythemia
- Discordant Hgb rare in TTTS
- Discordant weight common in TTTS
  - ? threshold of >20%
Twin-Twin Transfusion Syndrome

Diagnostic Evaluation

- Echocardiogram
- Fetal MRI
- Ultrasound
  - Monochorionic gestation
  - Oligohydramnios DVP < 2cm
  - Polyhydramnios DVP > 8 cm
  - Doppler velocimetry changes
    - Donor
      - AEDF in UA
      - Complete absence of DF in UA
    - Recipient
      - Pulsatile UV
      - AEDF in UA
      - DV: decreased, absent, reversed a wave
  - Growth discordance

- Echocardiogram
- Fetal MRI
- Ultrasound
TTTS DIAGNOSIS OF EXCLUSION

- 15% cases not TTTS
- TTTS mimicked by
  - Placental insufficiency
  - Dichorionic gestation
  - Discordant anomaly
  - Discordant viral infection
  - Klippel-Trenaunay-Weber
### Fetal MRI Findings in TTTS

<table>
<thead>
<tr>
<th></th>
<th>Recipient Cases</th>
<th>Donor Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrops/Ascites</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Brain Bleed/Ischemia</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Demise</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Twin-Twin Transfusion Syndrome

TTTS Cardiomyopathy
- Cardiac decompensation
- More afterload pathology
- Not volume stress
- Isolated tricuspid regurgitation
- RV hypertension  Systolic P> 80 mmHg
- Pulmonary outflow tract obstruction
- Pulmonary insufficiency
- Pulmonary atresia/intact ventricular septum
- Elevated Endothelin I
  - Fisk et al 1998
- Recipient twins hypertensive as newborns
  - Tolosa et al 1993
Echocardiographic Findings in TTTS

- Myocardial hypertrophy RV > LV
- Decreased compliance RV > LV
  - Monophasic inflow
- AV valve incompetence TV > MV
- Poor compliance/ AV valve incompetence reflected in
  - DV abnormalities
    - Decrease in a wave
    - Absence of a wave
    - Reversal of a wave
- Acquired congenital heart disease
  - Pulmonic valve stenosis, insufficiency, atresia
  - Not reversible with treatment of TTTS
Endothelin-1 Levels in TTTS

From Bajoria et al., Human Reproduction 1999; 14(6)
Endothelin precursor

Active hormones
- ET-1
- ET-2
- ET-3

Receptors
- Type A

Cells
- Vascular smooth-muscle cells
- Endothelial cells

Effects
- Vasoconstriction
- Cellular hypertrophy
- Cellular proliferation
- Vasodilation (via NO)
- Other effects e.g. ET gene expression
- Brain, kidney (man)

Preferred organs
- Heart, vessels
- Brain, kidney (man)
Renin-Angiotensin System (RAS) in TTTS

- **Circulating**
  - Kidney
  - Short-term effects
    - Sodium and water reabsorption via aldosterone secretion
  - Vessels
    - Vasoconstriction
  - Heart
    - Positive chronotropic effects and arrhythmogenic effects

- **Tissue**
  - Kidney
  - Long-term effects
    - Intraglomerular hypertension
  - Vessels
    - Vascular hypertrophy
  - Heart
    - Myocardial hypertrophy
Cardiac Sequelae: Recipient Twin

- Angiotension II
- ET-1

Hypertension

Cardiac Remodeling

- Early
- Late

Hypertrophy

- Diastolic Dysfunction
- Systolic Dysfunction

Impaired relaxation
Elevated filling pressures

Volume Overload

Further hypertrophy
Fibrosis? Apoptosis?

↓ Stroke volume
↓ Cardiac output

HYDROPS
Cardiac Sequelae in TTTS: Donor Twin

- Less *in utero* abnormality
- Abnormal postnatal arterial function
  - Decreased arterial distensibility
  - Related to vascular changes related to low vascular volume/flow?
  - Risk of later hypertension?
Quintero Staging of TTTS

Stage I: Discordant amniotic fluid: DVP >8 cm & < 2 cm

Stage II: Absent bladder in the donor

Stage III: Doppler velocimetry changes in UA, UV, DV

Stage IV: Hydrops

Stage V: Death of one fetus
Acute Cardiac Changes in TTTS

Quintero Staging

I  II  III        IV  V

Donor
AEDF in UA

Recipient
Severe biventricular failure
Reversal of flow in DV
Severe TR/MR
Reversal of flow in UA rec

Early TTTS

Endstage TTTS

Staging is heavily weighted toward the donor
Recipient findings on in advance stage III and IV
## Cardiovascular Profile Score (CVPS)

<table>
<thead>
<tr>
<th>Hydrops</th>
<th>Normal</th>
<th>-1 point</th>
<th>-2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td></td>
<td>Ascites, pleural</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pericardial effusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>skin edema</td>
</tr>
<tr>
<td>Venous Dopplers</td>
<td>Normal</td>
<td></td>
<td>DV atrial reversals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Venous pulsations</td>
</tr>
<tr>
<td>CT Ratio</td>
<td>≤ 0.35</td>
<td></td>
<td>&gt; 0.35 &lt; 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 0.5</td>
</tr>
<tr>
<td>Abnormal myocardial</td>
<td>Vent SF &gt; 0.28</td>
<td></td>
<td>SF &lt; 0.28</td>
</tr>
<tr>
<td>function</td>
<td>No AV regurg</td>
<td></td>
<td>TR or semi lunar</td>
</tr>
<tr>
<td></td>
<td>valve regurg</td>
<td></td>
<td>TR +dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>any MR</td>
</tr>
<tr>
<td>Abnormal Arterial</td>
<td>Normal</td>
<td></td>
<td>AEDF</td>
</tr>
<tr>
<td>Dopplers</td>
<td></td>
<td></td>
<td>REDF</td>
</tr>
</tbody>
</table>

**Cardiovascular Profile Score (CVPS). From Huhta, J Perinat Med 29:390-398, 2001**
NIH Sponsored TTTS Trial

Logistic Regression Analysis of Covariates on Survival

- **Recipients**
  - Cardiovascular Profile Score*
  - Most predictive of poor recipient outcome
    - OR = 3.025/point
    - p = 0.054

- **Donors**
  - Most predictive models of poor outcome
    - Increased Stage
      - OR = 0.446/stage p = 0.124
    - Earlier Gestational Age
      - OR = 1.052/day p = 0.097

*Huhta et al
Impact of Fetal Echocardiographic Findings on Recipient Survival

Cardiovascular Profile Score (CVPS)

- 62 consecutive recipient twins with TTTS
  - 3 stage IV
  - 26 stage III
  - 33 stage I or II
  - All patients treated by SFLP
  - All patients had pre-operative echo evaluated
  - Blinded to outcome

Recipient Survival Following SFLP Based on Pre-Operative CVPS

![Bar graph showing recipient survival rates with p-values: p<0.03 for 10 of 10 CVPS, p<0.008 for 9 of 10 CVPS.]
## Problem with the CVPS

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>-1 point</th>
<th>-2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrops</strong></td>
<td>None</td>
<td>Ascites, pleural skin edema</td>
<td>pericardial effusion</td>
</tr>
<tr>
<td><strong>Venous Dopplers</strong></td>
<td>Normal</td>
<td>DV atrial reversals</td>
<td>Venous pulsations</td>
</tr>
<tr>
<td><strong>CT Ratio</strong></td>
<td>(&lt; 0.35)</td>
<td>(&gt; 0.35&lt; 0.5)</td>
<td>(&gt; 0.5)</td>
</tr>
<tr>
<td><strong>Abnormal myocardial function</strong></td>
<td>No AV regurg</td>
<td>Vent SF (&gt; 0.28)</td>
<td>SF (&lt; 0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TR or semi lunar valve regurg</td>
<td>TR +dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>any MR</td>
</tr>
<tr>
<td><strong>Abnormal Arterial Dopplers</strong></td>
<td>Normal</td>
<td>AEDF</td>
<td>REDF</td>
</tr>
</tbody>
</table>


Not sensitive enough
TTTS Cardiomyopathy

- Fetal hypertensive cardiomyopathy
- 3 parameters of cardiomyopathy

  - AV valve competence
    - Mild, moderate, severe TR/MR
  
  - Hypertrophy
    - End-diastolic LV, RV, Septum

  - Myocardial dysfunction
    - Tei myocardial performance index
Cincinnati Modification of Quintero TTTS Staging

Stage I
Stage II
Stage III
  IIIA  Mild cardiomyopathy
  IIIB  Moderate cardiomyopathy
    IICSevere cardiomyopathy
Stage IV
Stage V
Echocardiographic Features of TTTS by Stage

Incidence of TR and MR

Cincinnati Stage

Tricuspid Regurgitation

Mitral Regurgitation
Echocardiographic Features of TTTS by Stage

Biventricular Hypertrophy

Incidence of Biventricular Hypertrophy

Cincinnati Stage

Percent

0 10 20 30 40 50 60 70 80 90 100

III IIIA IIIB IIIC IV

Biventricular Hypertrophy

Colorado Maternal Care Center
Assessing Recipient TTTS Cardiomyopathy

Tei Myocardial Performance Index

Tei C, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function--a study in normals and dilated cardiomyopathy. J Cardiol 1995;26:357-66


\[
\text{Index} = \frac{(a - b)}{b} = \frac{(ICT + IRT)}{ET}
\]

\[(a - b) = ICT + IRT\]

\[ICT = (a - b) - IRT\]

\[IRT = (c - d)\]

\[PEP \quad RV \quad Outflow\]

\[ET\]
Assessing Recipient TTTS Cardiomyopathy

Tei Myocardial Performance Index

* Identify subtle alteration in ventricular function
* Difficult to accurately measure
* Inter-observer variability can be high
* FCC echocardiographers 10% variation
* Minimal change is >10%
* Method to detect progression of TTTS during trial of AR
* Underestimates dysfunction in moderate TR/MR
* Can confirm post-treatment arrest of TTTS
Cincinnati Modification of Quintero TTTS Staging

Stage I
Stage II
Stage III

IIIA  RV MPI > 0.5 (Z+2) / LV MPI > 0.42 (Z+2)
     Mild ventricular hypertrophy (Z for RV/LV >2)
     Mild AV valve regurgitation

IIIB  RV MPI > 0.56 (Z+3) / LV MPI > 0.53 (Z+3)
     Moderate ventricular hypertrophy (Z for RV/LV >3)
     ≥ Mod AV valve regurgitation

IIIC  RV/LV > Z+4 Critical Doppler changes in RT (reversed a wave DV, reversed UA)
     Severe TR/MR, severe dysfunction

Stage IV
Stage V
Echocardiographic Features of TTTS by Stage

Tei Index

Cincinnati Stage

Myocardial Performance Index

LV MPI
RV MPI

III  IIIA  IIIB  IIIC  IV

0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8
Cincinnati Modification of Quintero TTTS Staging

TTTS cases since NIH Trial Closed May 2005

585 TTTS patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17.2%</td>
</tr>
<tr>
<td>II</td>
<td>10.3%</td>
</tr>
<tr>
<td>III</td>
<td>11.5%</td>
</tr>
<tr>
<td>IIIA</td>
<td>25.3%</td>
</tr>
<tr>
<td>IIIB</td>
<td>18.4%</td>
</tr>
<tr>
<td>IIIC</td>
<td>4.6%</td>
</tr>
<tr>
<td>IV</td>
<td>6.9%</td>
</tr>
<tr>
<td>V</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

48.3% + 59.8%
Distribution by Quintero Stage of TTTS Patients: The Fetal Care Center of Cincinnati
Shift in Stage Distribution Comparing Quintero and Cincinnati Staging Systems

Quintero vs Cinc

Stag

0  I  II  III  IIIa  IIIb  IIIc  IV  V

Quintero
Cincinnati
Percentage of Cases by Stage
Upstaged by Echocardiographic Findings

May 2005-January 2009

Percent Upstaged

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percent Upstaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60</td>
</tr>
<tr>
<td>II</td>
<td>70</td>
</tr>
<tr>
<td>III</td>
<td>90</td>
</tr>
</tbody>
</table>
Echocardiographic Upstaging of Stage I

Upstaging of Quintero's Stage I

70 patients

- Stage I: 39%
- Stage II: 61%
  - Stage IIIA: 27%
  - Stage IIIB: 14%
  - Stage IIIC: 20%

- Stage II: 39%
- Stage III: 61%
  - Stage IIIA: 27%
  - Stage IIIB: 14%
  - Stage IIIC: 20%

- Stage II: 39%
- Stage III: 61%
  - Stage IIIA: 27%
  - Stage IIIB: 14%
  - Stage IIIC: 20%

- Stage II: 39%
- Stage III: 61%
  - Stage IIIA: 27%
  - Stage IIIB: 14%
  - Stage IIIC: 20%
Echocardiographic Upstaging of Stage I

Upstaging of Quintero's Stage II

40 Patients

- Stage II: 36%
- Upstaged: 64%
  - Stage IIIA: 16%
  - Stage IIIB: 25%
  - Stage IIIC: 23%

Legend:
- Stage II
- Stage IIIA
- Stage IIIB
- Stage IIIC
The twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a cardiovascular score to assess severity of disease

Jack Rychik, MD; Zhiyun Tian, MD; Michael Bebbington, MD; Feng Xu, MD; Margaret McCann, BA; Stephanie Mann, MD; R. Douglas Wilson, MD; Mark P. Johnson, MD

- Qualitative findings
- 0-2 points added for progressive abnormality
- Described as quartiles for total score
- (1-4, mild to severe)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Finding</th>
<th>Numeric score</th>
<th>Fetuses with this finding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>Umbilical artery</td>
<td>Normal</td>
<td>0</td>
<td>96 (64%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased diastolic</td>
<td>1</td>
<td>34 (23%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absent/delayed diastolic</td>
<td>2</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>Recipient</td>
<td>Ventricular</td>
<td>Hypertrophy</td>
<td>0</td>
<td>77 (51%)</td>
</tr>
<tr>
<td></td>
<td>hyper trophy</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>1</td>
<td>73 (48%)</td>
</tr>
<tr>
<td></td>
<td>Cardiac dilation</td>
<td>None</td>
<td>0</td>
<td>78 (55%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>1</td>
<td>47 (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;mild</td>
<td>2</td>
<td>26 (17%)</td>
</tr>
<tr>
<td></td>
<td>Ventricular</td>
<td>dysfunction</td>
<td>None</td>
<td>117 (78%)</td>
</tr>
<tr>
<td></td>
<td>dysfunc tion</td>
<td>Mild</td>
<td>1</td>
<td>12 (8%)</td>
</tr>
<tr>
<td></td>
<td>Tricuspid valve</td>
<td>regurgitation</td>
<td>None</td>
<td>57 (38%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>1</td>
<td>31 (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;mild</td>
<td>2</td>
<td>12 (8%)</td>
</tr>
<tr>
<td></td>
<td>Mitral valve</td>
<td>regurgitation</td>
<td>None</td>
<td>191 (13%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>1</td>
<td>12 (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;mild</td>
<td>2</td>
<td>13 (9%)</td>
</tr>
<tr>
<td></td>
<td>Tricuspid valve</td>
<td>inflow</td>
<td>Double-peak</td>
<td>115 (78%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single-peak</td>
<td>1</td>
<td>37 (26%)</td>
</tr>
<tr>
<td></td>
<td>Mitral valve</td>
<td>inflow</td>
<td>Double-peak</td>
<td>135 (88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single-peak</td>
<td>1</td>
<td>15 (10%)</td>
</tr>
<tr>
<td>Ductus</td>
<td>Venosus</td>
<td>All antegrade</td>
<td>0</td>
<td>114 (76%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absent diastolic</td>
<td>1</td>
<td>13 (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood flow</td>
<td>2</td>
<td>23 (15%)</td>
</tr>
<tr>
<td></td>
<td>Unobstructed valve</td>
<td>No pulsations</td>
<td>0</td>
<td>136 (88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsations</td>
<td>1</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Right-sided outflow tract</td>
<td>Pulmonary artery &gt; sorts</td>
<td>0</td>
<td>126 (84%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary artery = sorts</td>
<td>1</td>
<td>12 (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary artery &lt; sorts</td>
<td>2</td>
<td>13 (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right ventricle</td>
<td>3</td>
<td>9 (6%)</td>
</tr>
<tr>
<td></td>
<td>right outflow</td>
<td>obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>regurgitation</td>
<td>None</td>
<td>0</td>
<td>145 (92%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>1</td>
<td>5 (3%)</td>
</tr>
</tbody>
</table>

From Rychik et al., Am J Obstet Gynecol 2007; 197
From Rychik et.al., Am J Obstet Gynecol 2007; 197
## Treatments for Twin-Twin Transfusion Syndrome

- Maternal Digoxin
- Maternal Indocin
- Maternal nifedipine
- Amnioreduction
- Selective fetocide
- Hysterotomy for cord ligation
- Sectio parva
- Blood letting of recipient
- Septostomy
- Microseptostomy
- Non-selective Laser photocoagulation
- Selective Laser photocoagulation
- Sequential selective laser photocoagulation
- Fetoscopic cord ligation
- Fetoscopic RFA
- Fetoscopic cord coagulation
Twin-Twin Transfusion Syndrome

Amniocentesis

- Standard therapy in US
- Initially treated maternal symptoms
- Survival of 50%
  - Moise Semin Perinatol 1993
- Survival in aggressive amnioreduction
  - 37% to 83%
- Minimal maternal or fetal risk
- Incidence of neurologic abnormalities
  - 18 to 26 % of survivors
Twin-Twin Transfusion Syndrome

- International Registry on TTTS Treated by Amnioreduction
- 223 pregnancies < 28 weeks
- Average number of amnioreductions 2
- Complications-mostly fetal
  - PPROM 6.2%
  - Labor 3.1%
  - Fetal demise 3.4%
  - Placental abruption 1.3%
  - Chorioamnionitis 0.9%
  - Miscarriage 0.4%
Twin-Twin Transfusion Syndrome

- Survival to birth 78%
- Survival to 4 weeks of age 60%

International Amnioreduction Registry
Mari et al
## Twin-Twin Transfusion Syndrome

### Neonatal Co-Morbidity

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Recipient (n=109/144)</th>
<th>Donor (n=88/122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH Grade 3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IVH Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IVH (Unclassified)</td>
<td>5 (1*)</td>
<td>5 (1*)</td>
</tr>
<tr>
<td>Ventricular dilation</td>
<td>12 (8 mild; 1 moderate; 3 unclassified) (6*)</td>
<td>12 (7 mild; 3 moderate; 2 unclassified) (8*)</td>
</tr>
<tr>
<td>Cerebral echogenic foci</td>
<td>6 (3*)</td>
<td>8 (4*)</td>
</tr>
<tr>
<td>Cerebral Cysts</td>
<td>4 (2*)</td>
<td>1 (1*)</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>4 (3*)</td>
<td>6 (2*)</td>
</tr>
<tr>
<td>Porencephaly</td>
<td>1 (1*)</td>
<td>0</td>
</tr>
<tr>
<td>Multilocular encephalomalacia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>0</td>
<td>1 (1*)</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Schizencephaly</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The numbers with asterisk indicate that the twins had more than one brain abnormality; IVH = intraventricular hemorrhage

From Mari G, Roberts A, Detti L, et al: Perinatal morbidity in severe twin twin transfusion syndrome: Results of the International Amnio reduction Registry (see appendix)
## Twin-Twin Transfusion Syndrome

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Recipient (n=144)</th>
<th>Donor (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome</td>
<td>63 (43.7%)</td>
<td>47 (38.5%)</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac structural abnormality</td>
<td>5 PS</td>
<td>1 DORV, VSD, PS</td>
</tr>
<tr>
<td></td>
<td>2 Tricuspid valve abnormality</td>
<td>1 ASD, PS;</td>
</tr>
<tr>
<td></td>
<td>4 PDA</td>
<td>1 VSD and PDA, 3 PDA</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Amputation 1 foot</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cleft lip/palate</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Meconium peritonitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Talipes</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
SEPTOSTOMY

- Single amnioreduction paradox
- Inadvertent septostomy
  - Saade et al Fetal Diagn Ther 13:868-93
    - 12 patients
    - Survival 83% at GA of 31 wks
    - 7 patients
    - Survival 57%
    - Single institution: 7 cases AR; 7 cases septostomy
    - Survival for AR 64%:
    - Survival for septostomy 71%
- Moise et prospective trial comparing AR to septostomy
  - 65% survival with AR and with septostomy
Twin-Twin Transfusion Syndrome

Placental Pathology

- Chorioangiopagus
  - 83% of 296 monochorionic placentas
- Multiple inter-twin vascular connections
  - DeLia et al 9-10 vessels
- Bajoria and Fisk
  - A-V vascular connections
  - Few in number & deep
  - Net imbalance in flow
Twin-Twin Transfusion Syndrome

Non-Selective Fetoscopic Laser Photocoagulation

- **1990 DeLia**
  - Obstet Gynecol 75:1046, 1990
- **1995 DeLia**
  - 53% survival
  - 96% “developing normally”
- **1995 Ville**
  - N Engl J Med 332;224, 1995
  - 53% survival
  - Survivors “developing normally”
# Twin-Twin Transfusion Syndrome

Non-Selective or Semi-Selective
Fetoscopic Laser Photocoagulation

<table>
<thead>
<tr>
<th></th>
<th>Fetal Survival</th>
<th>At least 1 Survivor</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeLia '95</td>
<td>52.8%</td>
<td>69.2%</td>
</tr>
<tr>
<td>DeLia '99</td>
<td>69%</td>
<td>82%</td>
</tr>
<tr>
<td>Ville '98</td>
<td>54.5%</td>
<td>73.5%</td>
</tr>
<tr>
<td>Senat '04</td>
<td>57%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Inter-twin Membrane
Twin-Twin Transfusion Syndrome

Selective Fetoscopic Laser Photocoagulation

1998 Quintero et al

1999 Hecher et al
- 73 Fetoscopic laser
- 43 Amnioreduction
- Survival: Laser 61% AR 51%
- Both in same pregnancy 54%
- One or both survive 79% vs 60%
- Abnormal brain US 6% vs 18%
## Twin-Twin Transfusion Syndrome

### Selective Fetoscopic Laser Photocoagulation

<table>
<thead>
<tr>
<th></th>
<th>Fetal Survival</th>
<th>At least 1 Survivor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecher ‘99</td>
<td>61%</td>
<td>79%</td>
</tr>
<tr>
<td>Hecher ‘00</td>
<td>68%</td>
<td>81%</td>
</tr>
<tr>
<td>Quintero ‘00</td>
<td>61.3%</td>
<td>83%</td>
</tr>
<tr>
<td>Quintero ‘03</td>
<td>64.2%</td>
<td>83.2%</td>
</tr>
<tr>
<td>Huber ‘04</td>
<td>70%</td>
<td>83%</td>
</tr>
<tr>
<td>Huber ‘06</td>
<td>71.5%</td>
<td>83.5%</td>
</tr>
<tr>
<td>Crombleholme ‘07</td>
<td>77%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Crombleholme ‘12</td>
<td>89%</td>
<td>95%</td>
</tr>
</tbody>
</table>

![Diagram of fetal vessels](image)

- Vascular Equator
- Inter-twin Membrane
## Impact of Complications on Survival

<table>
<thead>
<tr>
<th></th>
<th>No complication</th>
<th>Early complication</th>
<th>Late complication</th>
<th>Both</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at procedure</td>
<td>21.0 ± 2.5</td>
<td>21.3 ± 2.6</td>
<td>21.1 ± 2.4</td>
<td>22.2 ± 2.5</td>
<td>N.S</td>
</tr>
<tr>
<td>GA at delivery (weeks)</td>
<td>31.4 ± 4.1</td>
<td>28.3 ± 5.7</td>
<td>30.1 ± 3.1</td>
<td>29.8 ± 3.8</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Numbers DA-RV anastomoses</td>
<td>6.8 ± 6</td>
<td>4.5 ± 3.5</td>
<td>6.9 ± 4.4</td>
<td>3.7 ± 1.9</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Total number of anastomoses coagulated</td>
<td>13.4 ± 8.5</td>
<td>9.9 ± 6.4</td>
<td>14.3 ± 8.9</td>
<td>9.57 ± 6.4</td>
<td>N.S</td>
</tr>
<tr>
<td>Survival of one or both twins</td>
<td>96.7%</td>
<td>70.2%</td>
<td>84.7%</td>
<td>53.3%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Recipient survival</td>
<td>92%</td>
<td>59.6%</td>
<td>83.1%</td>
<td>46.7%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Donor survival</td>
<td>88.5%</td>
<td>48.9%</td>
<td>66.1%</td>
<td>33.3%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Solomon Technique

- 15 to 25% residual connections
- 13-15% incidence of persistent TTTS
- 13-15% incidence of TAPS
- Technique to connect the dots
- Photocoagulation between connections
- Markedly decreased missed vessels
Mapping protocol

1st
Identification of all vascular connection and recorded the findings.

2nd
Confirmation of the vascular connection and laser photocoagulation.

3rd
No vascular connection was missed and no vessel had recanalized.

Incidence of persistent/recurrent TTTS: < 1%
Incidence of TAPS: <<1%
Twin-Twin Transfusion Syndrome

Sequential Selective Fetoscopic Laser Photocoagulation

- Sequential selective laser photocoagulation of communicating vessels in twin-twin transfusion syndrome
- Donor AV first, then Recipient AV then A-A then V-V
- Favorable results
- Likely due to detailed mapping
- Shorter duration of laser use
Can Donor Survival be Improved by Operative Technique?

- Donor survival dependent on placental share
- Broad range of placental share for donor by
  - 95% less than recipient share
- Magisterial vascular pattern
- Acute placental insufficiency results in donor demise
- Chronic placental insufficiency results in growth restriction
Impact of Laser Time on Survival

![Bar chart showing the impact of laser time on survival]

- Survival of 1
- Recipient
- Donor
- # of Vessels

Colors:
- Blue: < 5 min
- Yellow: 5-10 min
- Maroon: > 10 min

Significance Levels:
- *p < 0.05
- **p < 0.001
Can Adjunctive Medical Therapy Improve Recipient Survival in TTTS Cardiomyopathy?

* NIH Trial-importance of echocardiographic findings
* Fetal anti-hypertensive agent?
* Can’t use ACE inhibitors or ET1 receptor blockers
* ? Nifedipine
  * Commonly used tocolytic agent
  * Most commonly used anti-hypertensive agent in pregnancy
  * Fetal cord blood levels 93% of maternal venous levels
  * Amniotic fluid levels 53% of maternal venous levels
Case Control Observational Study of Nifedipine in TTTS-Cardiomyopathy

- Empiric treatment of TTTS cardiomyopathy with nifedipine 20 mg q 6 hours
- Stages IIIA, IIIB, IIIC, IV
- 20 mg q 6 hours 24-48 hours pre-SFLP
- 141 TTTS cases
- 152 control cases
  - Matched 2:1 when possible
  - Matched for GA
  - Matched for Cincinnati Stage
- Nifedipine treated group
  - 61.0% stage IIIC and IV
  - 29.6% for controls, p<0.001
- Significant reduction in tocolytics
Acute Post-Operative Recipient Fetal Survival

* \( p < 0.017 \)
Recipient Survival to Birth

**

- All Stages: 83 (Nifedipine), 75 (Control)
- State IIIA: 100 (Nifedipine), 83 (Control)
- Stage IIIB: 90 (Nifedipine), 72 (Control)

Nifedipine
Control
*=p≤0.03
Effect of Nifedipine on Survival in TTTS Treated by SLFP

- No survival benefit in Stage IIIC and IV
  - More favorable cases used as controls
  - As a result better than expected control survival in Stage IIIC/IV
- No survival benefit in donors at any stage
- Retrospective nature of study
- Can’t prove recipient survival benefit is due to nifedipine
- Need prospective randomized trial
Among 451 TTTS evaluated from 2005 to 2009

- 123(27%) cases of Quintero stage I (n=77, 63%) stage II (n=46, 37%).

- 65 % (n=80) elected expectant management
  - A trial amnioreduction (n=67)
  - Observation (n=13)

- 35% (n=43) had primary SFLP.
Rate of Progression in TTTS Managed by Observation or AR

- Progression in 54% (43/80)
- No progression in 46% (37/80)
- Progression was identified by ultrasound and/or fetal echocardiography at a mean duration of 1.4±1.5 weeks
- Progression was treated with SFLP
Progression among Quintero stages I + II treated with amnioreduction or observation initially as a function of recipient cardiomyopathy.
Prospectively studied Sequential Therapy in TTTS cases without or with mild RT cardiomyopathy

585 TTTS cases
212 Stages I, II, III or IIIA

AR/Observation (n=158)
Weekly US and Echo

Progression

Responder

• Recurrence of polyhydramnios
• Worsening Doppler flow studies
• Worsening recipient echocardiographic parameters.
  • Artrioventricular valve
  • Ventricular Hypertrophy
  • MPI>10% from initial values

SFLP
Results

- 62% (n=98/158) was the overall response rate
  - 81% in Observation (n=38/47)
  - 55% in trial of amnioreduction (n=60/111)

- Progression was diagnosed:
  - 45% echocardiographic progression
  - 32% by only ultrasound
  - 23% by both echocardiography and ultrasound
212 TTTS patient with no or mild recipient cardiomyopathy

TTTS patient treated by either AR or OBS
n=158/212 (75%)

TTTS patient treated by primary SFLP
n=54/212 (25%)

Initial Treatment

AR
N=111/212 (53%)

OB
n=47/212 (22%)

Primary SFLP
n=54/212 (25%)

Progression of TTTS

NO
n=60/111 (55%)

Yes
n=51/111 (45%)

Yes
n=9/47 (19%)

NO
n=38/47 (81%)

Sequential therapy

Sequential Therapy
n=60/158 (38%)

Fetal Survival

Primary AR
103/120 (86%)

Sequential
95/120 (79%)

Primary OBS
66/76 (87%)

Primary SFLP
87/108 (81%)
Complications after Amnioreduction (n=111)

• 22/111 patients treated with amnioreduction.
  - 8% (n=9) chorioamnio-separation
  - 2% abruption
  - 3% PPROM
  - 7% pregnancy loss <24 weeks.

• Among those 9 patients with detectable CAS,
  - 7 were candidate for SFLP due to disease progression
  - SFLP done in 5
  - Only 2 patients could not have SFLP
Trial of Amnioreduction vs Selective Fetoscopic Laser Photocoagulation

- AR responders survival
  - 82.2% overall survival
  - 90.7% 1 or both surviving
  - 75% both surviving

- AR non-responders-SFLP
  - 79.5% overall survival
  - 89.9% 1 or both surviving
  - 70% both twin survive
Conclusions

- TTTS is a hemodynamic derangement
- TTTS cardiomyopathy central to pathophysiology
- Cincinnati and CHOP systems incorporate cardiac changes into staging
- Nifedipine may be first effective adjunctive medical Rx for TTTS
- Laser time determinate of donor survival
Challenges in TTTS

- Define the etiology
- Improving survival
  - Develop targeted medical therapies
  - Adjunctive medical therapy in AR
- Reducing morbidity
  - Defining cases that need treatment
  - Cerclage?
  - Extend the length of gestation
- Outcomes driven management