Recognition and Management of Twin-Twin-Transfusion Syndrome

Michael A. Belfort, MBBCH, MD, PhD

Chairman and Professor of Ob/Gyn
Baylor College of Medicine
Houston, Texas

Obstetrician and Gynecologist-in-Chief
Texas Children’s Hospital
I have no conflict of interest to declare
Disclaimer

Mead Johnson sponsors programs such as this to give healthcare professionals access to scientific and educational information provided by experts. The presenter has complete and independent control over the planning and content of the presentation, and is not receiving any compensation from Mead Johnson for this presentation. The presenter’s comments and opinions are not necessarily those of Mead Johnson. In the event that the presentation contains statements about uses of drugs that are not within the drugs' approved indications, Mead Johnson does not promote the use of any drug for indications outside the FDA-approved product label.
Twins

Normal

Abnormal

Texas Children's Fetal Center

BCM
Baylor College of Medicine
Twins Statistics

1.2% of births in the USA are twins (1:80 – 1:90):
- 30% are identical (monozygotic) – 0.4% of all births
  - 25% of these are dichorionic / 75% monochorionic
  - 3/1000 (0.3%) of all births monochorionic
- 70% are fraternal (dizygotic), 50% are same sex
  ~ 100% are dichorionic

Odds of having identical twins are 4/1000 (1:250), monochorionic 3/1000

Identical twins are not familial and consistent across racial/ethnic/geographic groups
Twins and Zygosity

Zygosity - degree of identity in the genome of twins:

Monozygotic (single sperm and egg - identical) – 8%
Dizygotic (2 eggs/sperm - fraternal or sororal) – 92%

Chorionicity – number of placentas

25% of monozygotic twins are dichorionic (2 placentas)
75% of monozygotics share a single placenta (monochorionic)

Very rarely dizygotic twins can become monochorionic –
blastocyst fusion

2% of monozygotics are monamniotic
Interesting Twin Facts

1. Monozygosity – 0.3% (3/1000) of all births – random event – spontaneous collapse of the blastocyst with splitting of progenitor cells in two

2. Dizygosity – genetically heritable – variable rates in different populations – 6/1000 in Japan, 30/1000 in USA

3. Monozygotic twins may appear phenotypically different – environmental or different X inactivation

4. Epigenetic modification over time – environmental factors – 50 yr olds have 3X the differences of 3 yr olds

5. Half-twins – different paternal DNA - same maternal DNA
<4 d 4-8 d 8-14 d 14-18 d

Morula

Blastula

Blastocyst

Dichorionic Diamniotic

Monochorionic Diamniotic

Monochorionic Monoamniotic

Conjoined
Monochorionic Twins

Normal

Abnormal
The hidden mortality of monochorionic twin pregnancies

Survival

Dichorionic vs. Monochorionic twins

Dichorionic vs. “Apparently normal” Monochorionic twins

Lee et al. Obstet Gynecol 2008
Pathophysiology of TTTS

Traditionally thought of as a net unidirectional flow or pressure differential through abnormal vascular connections – 1-2/10,000 births
SUPERFICIAL ANASTOMOSES

Artery to Artery
Vein to Vein
DEEP ANASTOMOSES

Artery to Vein
Artery on top of Vein
Monochorionic Twins
Pathophysiology of TTTS

- Comparison of 21 placentas from TTTS cases vs. 49 uncomplicated monochorionic twins

  - ↓ # of AA connections in TTTS

  - > one AV connection with no corresponding AA = 78% incidence of TTTS

Monochorionic Twins/
Pathophysiology of TTTS
Pathophysiology of TTTS

- All MC placentas have multiple vascular connections

  BUT

- only 5 – 15% of MC twins get TTTS……..1-2/10,000 births
Theories as to why TTTS Develops
Fetal, Local Placental as well as Maternal: Placental interface

- Recipient has higher ANP and endothelin-1 than donor
  - leads to cardiac failure in recipient
- Over-expression of renin in the donor’s kidneys and accelerated atherosclerosis (glomeruloendotheliosis) in the recipient’s kidneys – cf: preeclampsia
- Lower leptin and IGF-II in the recipient twin with metabolic dysfunction and increased resistance in donor placenta – IUGR in donor
Theories as to why TTTS Develops
Fetal, Local Placental as well as Maternal: Placental interface

Maternal: Higher maternal levels of anti-angiogenic factors (s-Flt-1 and endoglin), and lower maternal PIGF – suggests hypoxia and hypoperfusion of donor villi in the placenta as precipitating cause of TTTS rather than a primary abnormality in the placental circulation in a subset of TTTS
Renin Secretion

Renal Tubular Dysgenesis

ANGIOTENSIN

Maternal sflt/endoglin and PIGF - ??

Texas Children's Fetal Center

Mahieu Caputo 2000
RECIPIENT HEMODYNAMICS

- Hypertension, hypervolemia
  - High cardiac output
  - Peripheral Vasoconstriction

- Myocardial Hypertrophy
  - Coronary artery relaxation

- Oxygen Consumption

- End-Diastolic Pressure

- Myocardial Compliance
Diagnostic Criteria

- Oligo/anhydramnios
- Polyhydramnios
- Polyuria
- Oliguria
- Hypervolemia
FETAL HYPERTENSION

Renal vasoconstriction
Diagnosis of TTTS

Essentials for making the diagnosis:

- make sure it is monochorionic twins
- exclude anatomic anomalies
- consider aneuploidy in one twin
- infectious etiology (Parvo virus?)
- consider placental abruption or abnormal implantation, abnormal cord insertion
- exclude PPROM
- look for unequal placental sharing
Recognition of TTTS

• Unequal fluid volumes in DA/MC twins
  • Must have true polyhydramnios and oligohydramnios to make the diagnosis in most cases:
    DVP > 8 cm in the recipient (>10cm after 20 weeks)
    DVP < 2cm in the donor
  • Easily confused by “bell-clanger” baby
  • May be rare cases of a large A-A communication (fistula) that shows cardiac effects before renal shutdown (i.e before oligo/poly)
# TTTS Pre-operative Staging

<table>
<thead>
<tr>
<th>Stage I.</th>
<th>Poly/Oligohydramnios with bladder of the Donor still visible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II.</td>
<td>Bladder of the Donor not visible</td>
</tr>
<tr>
<td>Stage III.</td>
<td>Presence of either AEDF in the UA, reverse flow in the DV, or pulsatile UV in either twin (Tricuspid Regurgitation)</td>
</tr>
<tr>
<td>Stage IV.</td>
<td>Hydrops in either twin</td>
</tr>
<tr>
<td>Stage V.</td>
<td>Demise of one or both twins</td>
</tr>
</tbody>
</table>

*Quintero et al 1999*
**Twin-Twin-Transfusion Syndrome**

- **Chronic TTTS**
  - slower and later onset, minimal discordance
  - ? fewer connections
  - usually more widespread cord insertion

- **Acute TTTS**
  - sudden onset, usually acute polyhydramnios
  - more likely to be endocrine origin
  - may be precipitated by IUGR or another twin complication (unequal sharing)
TTTS vs. Unequal Sharing

• Unequal Placental Sharing often confused with TTTS
• Severe IUGR, oligohydramnios, small bladder in one baby, with other baby of normal size and with normal fluid (No Poly)
• Always > 20% discordance (frequently 30-40%)
• May be the catalyst for, or coexist with, acute TTTS
• Usually eccentric/velamentous cord insertion
• Laser ablation may not prevent death of the donor BUT will usually protect the recipient/normal baby
• Look for > 20% discordance with borderline polyhydramnios and oligohydramnios
• Doppler more likely to be abnormal in the smaller baby than the larger one (cf: opposite in TTTS)
Treatment of TTTS

- Consider options based on:
  Viability and severity of condition
  EGA at time of diagnosis
  Evidence of fetal damage/anomalies
- Explain all treatment options available under the circumstances
- Refer for perinatal consult ASAP
- Dictate a clear note on all discussions
Surveillance

- Mild or suspected T-T-T-S:
  - Close monitoring with serial US
    Frequency: individualize
  - Look at:
    - fetal weight disparity
    - relative amniotic fluid volumes
    - relative fetal bladder size
    - evidence of effusions
    - development of signs of hydrops
    - cord Doppler diastolic flow/NST/BPP
    - cervix
Advanced Surveillance:

- Ductus venosus Doppler
- Aortic isthmus Doppler
- MCA Doppler
- Urine production rate/bladder volume
- Cardiac size and PA pressure
- Tricuspid regurgitation
- Umbilical venous flow rate
- Umbilical vein diameter

Texas Children's Fetal Center

Baylor College of Medicine
Management

- Mild or suspected T-T-T-S:
  - Very Preterm - previable:
    set limits for intervention/admission
    consider prophylactic steroids at 24 weeks

- Viable but still Preterm:
  consider deliberate preterm delivery and NICU management versus delayed delivery
  make sure steroids are given if < 34 wks
  transfer to specialist center if necessary
Management

• Severe T-T-T-S:
  • Need for therapy versus early delivery
    Individualize
    In-house management for viable babies

• Therapeutic Options:
  delivery (especially for dying twin)
  serial amnioreduction
  amniotic septostomy
  laser therapy
  cord coagulation
Serial Amnioreduction

- Amnion of fetus "a"
- Chorion
- Amnion of fetus "b"
Serial Amnioreduction

- **Survival rates** reported as between 37-60%
  - May be ↑ because of selection bias (mild TTTS)

- **Subsequent neurologic injury** ~35%

- **Procedure-related complications** ~10%
  - Including pPROM, abruption, IUFD

Septostomy
Septostomy
Septostomy
Septostomy

- **Survival rates** as high as 83%
- Few data on subsequent neurologic outcome
- **Appears safe**
- Major risk is cord entanglement
- **No better than serial amnioreduction** *

Moise KJ Jr, et al. *Am J Obstet Gynecol* 2005; 193:701-7 (RCT; stopped after 73/140 subjects; no difference in survival of at least one fetus – 78 vs 80%; fewer procedures needed)
Laser Photocoagulation
Incomplete Ablation
“Solomonizing” – to avoid the small connections
Survival of at least one twin to 6 months

*Median 20 (6 - 42) Months*

Laser

55/72 (76.4%) v. 36/70 (51.4%)

RR: 1.49 [95% CI: 1.14 - 1.93]  
P = 0.002
# Monochorionic Twins/ Laser vs. Amnio for TTTS

## TABLE 3
Metaanalysis of overall survival rate

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>LASER*</th>
<th>AMNIORREDUCTION*</th>
<th>Weight (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1999</td>
<td>89/146</td>
<td>44/86</td>
<td>38.44%</td>
<td>1.4904 (0.8704 to 2.5822)</td>
</tr>
<tr>
<td>B</td>
<td>2004</td>
<td>81/136</td>
<td>54/136</td>
<td>37.87%</td>
<td>2.1579 (1.3319 to 3.496)</td>
</tr>
<tr>
<td>C</td>
<td>2006</td>
<td>48/62</td>
<td>32/54</td>
<td>13.02%</td>
<td>2.3571 (1.0532 to 5.2757)</td>
</tr>
<tr>
<td>D</td>
<td>2007</td>
<td>89/116</td>
<td>22/42</td>
<td>12.67%</td>
<td>2.9066 (1.4264 to 6.2999)</td>
</tr>
<tr>
<td>META-ANALYSIS:</td>
<td>307/452</td>
<td>152/318</td>
<td>100%</td>
<td>2.0469 (1.5172 to 2.7615)</td>
<td></td>
</tr>
</tbody>
</table>

* total n. of survivors / total n. of fetuses

OR: odds ratio; CI: Confidence Interval
test of heterogeneity: Q=2,51; P=0.47; I^2=0%

# Monochorionic Twins/
Laser vs. Amnio for TTTS

**TABLE 4**
Metaanalysis of neonatal death

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>LASER *</th>
<th>AMNIOREDUCTION *</th>
<th>Weight (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1999</td>
<td>0/65</td>
<td>7/51</td>
<td>11.53%</td>
<td>0.4238 (0.1344 to 1.3306)</td>
</tr>
<tr>
<td>B</td>
<td>2004</td>
<td>12/144</td>
<td>41/140</td>
<td>51.51%</td>
<td>0.2195 (0.1097 to 0.4394)</td>
</tr>
<tr>
<td>C</td>
<td>2006</td>
<td>3/62</td>
<td>9/54</td>
<td>12.37%</td>
<td>0.2542 (0.0651 to 0.9935)</td>
</tr>
<tr>
<td>D</td>
<td>2007</td>
<td>12/101</td>
<td>14/36</td>
<td>24.58%</td>
<td>0.2119 (0.0966 to 0.5218)</td>
</tr>
</tbody>
</table>

**META-ANALYSIS:**
33/402 (8.25%) 71/281 (25.21%)

\[
Z_{5.91}; P<0.0001
\]

* number of infants death / total number of infants
OR: odds ratio; CI: confidence interval
* test of heterogeneity: Q=1.07; P=0.78; I²: 0%

Monochorionic Twins/
Laser vs. Amnio for TTTS

Months from treatment
Laser Photocoagulation Outcome

TTTS Outcomes of Delivered Patients

- 69% DELIVERED 2
- 22% DELIVERED 1
- 9% DELIVERED 0

180 patients

91% delivered at least 1 fetus

Texas Children’s Fetal Center

Baylor College of Medicine
# Monochorionic Twins
## TTTS Neurologic Outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Percent follow-up</th>
<th>Age @ follow-up</th>
<th>Normal</th>
<th>Minor abnormal</th>
<th>Major abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banek *</td>
<td>89</td>
<td>100%</td>
<td>21 mo</td>
<td>78%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Graef *</td>
<td>167</td>
<td>98%</td>
<td>38 mo</td>
<td>87%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Lopriore #</td>
<td>82</td>
<td>100%</td>
<td>24 mo</td>
<td>83%</td>
<td>—</td>
<td>17%</td>
</tr>
<tr>
<td>Lopriore #</td>
<td>212</td>
<td>94%</td>
<td>24 mo</td>
<td>82%</td>
<td>—</td>
<td>18%</td>
</tr>
</tbody>
</table>

* Griffiths’ Developmental Test Scales; Snijders-Oomen Non-Verbal Intelligence Test
# Bayley’s Scales of Infant Development

Monochorionic Twins
Learning Curve of Laser
Monochorionic Twins
Unequal Placental Sharing without TTTS

• 15% of monochorionic twins
• One twin with normal growth and amniotic fluid
• Second twin with IUGR and oligo
• Related to unequal placental sharing
Selective IUGR
Monochorionic Twins
Selective IUGR

- No real treatment
  - Observation
  - Selective reduction
  - Laser ablation of placental anastomoses
  - Bipolar coagulation of the IUGR baby’s cord
Bipolar Umbilical Cord Occlusion
# Monochorionic Twins
## Selective IUGR

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Laser*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Gest Age @ delivery</td>
<td>31.0</td>
<td>32.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Survival of IUGR twin</td>
<td>25/31 (81%)</td>
<td>6/18 (33%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Survival of co-twin</td>
<td>29/31 (94%)</td>
<td>17/18 (94%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Survival of both twins</td>
<td>25/31 (81%)</td>
<td>5/18 (28%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVL in co-twin</td>
<td>4/28 (14%)</td>
<td>1/17 (6%)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

* Laser only possible in 88% of cases; 12% required second laser procedure

Gratacos et al. Ultrasound Obstet Gynecol 2008;31:669-75
Take-home points

• Monochorionic twins are **HIGH RISK** (monitor more frequently than dichorionic twins)

• Observe Stage I TTTS in the second trimester (weekly ultrasounds)

• Laser ablation is the treatment of choice for Stage II - IV TTTS between 16-26 weeks’ gestation

• sIUGR in dichorionic twins or in monochorionic twins after a viable age should be managed conservatively