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Twin to Twin Transfusion Syndrome

Saul Snowise, M.D.

"Soapbox" Moment

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"There is no diagnosis of '**twins**'.

The only diagnosis is a monochorionic or dichorionic twin gestation.

This should be clearly noted in the chart at 8 - 10 weeks".

Management of Monochorionic Gestations

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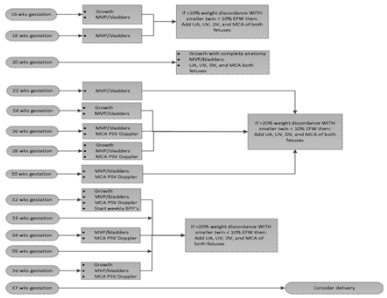

Risks of Monochorionic Gestations

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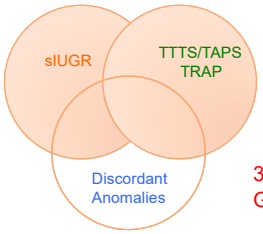

30% Monochorionic Gestations Affected

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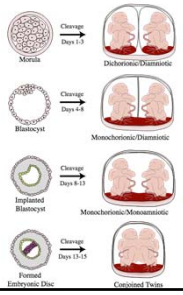
Dizygotic

Monozygotic



Incidence of Twins in U.S.

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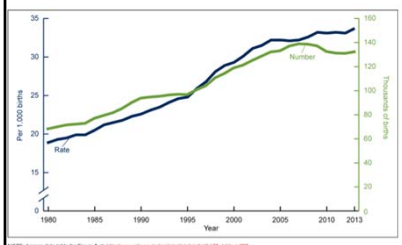

Dizygotic:Monozygotic ~ 3:1

MZ: Monochorionic:Dichorionic ~3:1

ART 1/30 vs Spontaneous Twins 1/350

US Live births 4,112,052 → 11,750 MCDA cases/yr

TTTS: Epidemiology

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9-15% of MCDA gestations
1:58 Twin pregnancies
1:4,170 pregnancies

4,112,052 → 11,750 MCDA cases/yr → 1,762 TTTS/yr

Presentation < 24 weeks ≥90% perinatal mortality

Dickinson et al. Am J Obstet Gynecol 2000;182:706-12
Saunders et al. Am J Obstet Gynecol 1992;166:820-4

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Twin to Twin Transfusion: Pathophysiology, Diagnosis and Staging

TTTS: Pathophysiology

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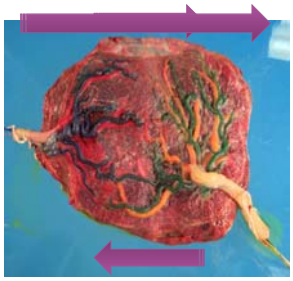

TTTS: Pathophysiology

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Donor	**Recipient**
Hypovolemia	Hypervolemia
Decreased urine output	Increased urine output
Decreased amniotic fluid	Increased amniotic fluid
Increased RAS activity ⟷	Increased ANP/BNP

TTTS: Pathophysiology

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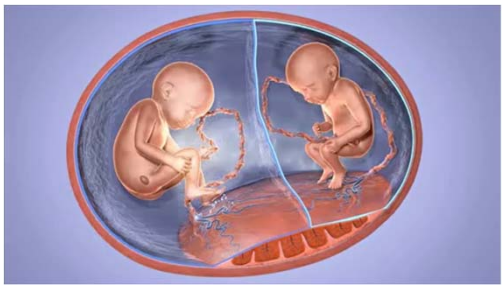

TTTS: Quintero Staging

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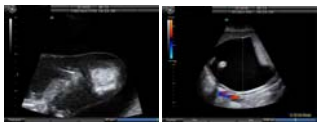
Stage 1
Donor MVP <2 cm;
Recipient MVP >8-10 cm



Stage 2
Absent bladder in donor twin; normal Doppler studies

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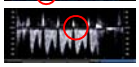
TTTS: Quintero Staging

Stage 3

	Normal	Abnormal
Umbilical Artery		
Umbilical Vein		
Ductus Venosus		
Middle Cerebral Artery		

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TTTS: Quintero Staging

Stage 4

Stage 5 Death of 1 or both fetuses

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TTTS: Cincinnati Cardiac Scoring Criteria

Table 1

Cardiovascular Profile Score (CVPS)(17, 18)

	Normal (2 points)	−1 point	−2 points
Hydrops Fetalis	None	Ascites, pleural effusion, or pericardial effusion	Skin edema
Abnormal Venous Doppler	Normal venous Doppler	Ductus venosus atrial systolic reversal	Umbilical venous pulsations
Cardiomegaly (CT ratio=cardiac area/thoracic area)	CT ratio ≤ 0.35	CT ratio >0.35 & <0.50	CT ratio >0.50
Abnormal myocardial function	Ventricular SF >0.28 & no valve regurgitation	SF <0.28 or TR or semilunar valve regurgitation	TR + dysfunction or any MR
Abnormal Arterial Doppler	Normal umbilical artery diastolic flow	Absent end-diastolic flow in the umbilical artery	Reverse end-diastolic flow in the umbilical artery

CT, cardiothoracic; MR, mitral regurgitation; SF, shortening fraction; TR, tricuspid regurgitation

Shah et al 2008

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TTTS: CHOP Cardiac Scoring Criteria

CHOP Cardiovascular Score *Scoring: Mild = 0-4, Moderate = 5-9, Moderate-severe = 10-14, Severe = 15-20*

Recipient Twin		0	1	2	3
Ventricular Characteristics	Cardiac Enlargement	None	Mild	>Mild	
	Vent Hypertrophy	None	Present		
	Systolic Dysfunction	None	Mild	>Mild	
Valve Function	Tricuspid Regurgitation (TR)	None	Mild	>Mild	
	Mitral Regurgitation (MR)	None	Mild	>Mild	
Venous Doppler Characteristics	Tricuspid Valve Inflow	2 Peaks	1 Peak		
	Mitral Valve Inflow	2 Peaks	1 Peak		
	Ductus Venosus	All Forward	Decreased Atrial Contraction	Reversal	
	Umbilical Vein Pulsation	None	Present		
Great Vessel Analysis	Outflow Traces	Pulmonary Artery (PA) = Aorta (Ao)	PA > Ao	PA < Ao	RV Outflow Obstruction
	Pulmonary Insufficiency	None	Present		
Donor Twin					
Umbilical Artery (UA) Doppler		Normal	Decreased Diastolic Flow	Absent or Reversed Diastolic Flow	

Rychik et al 2007

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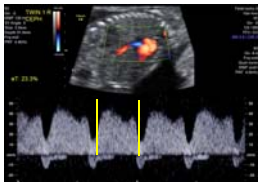
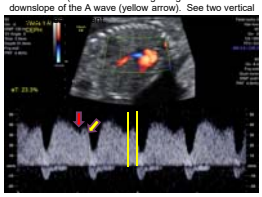
Diastolic Dysfunction In "Recipient" Twins

Measure total time interval of the ductus waveform (between yellow lines)



Measure the passive inflow from the notch between the S and A waves (red arrow to the beginning of the downslope of the A wave (yellow arrow). See two vertical



Calculate the % by dividing the time interval of the inflow by the total time interval. 0.093/0.400 = 23.3%

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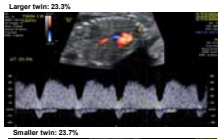
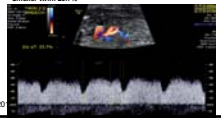
Diastolic Dysfunction In "Recipient" Twins

Selective IUGR scenario
(time intervals of smaller twin and larger twin are < 5% different

Larger twin: 23.3%

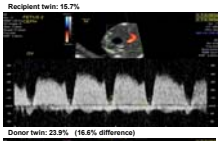


Smaller twin: 23.7%

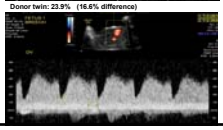


Twin-Twin Transfusion Scenario
(greater than 5% difference between time intervals; recipient with shorter passive filling phase)

Recipient twin: 15.7%



Donor twin: 23.9% (16.6% difference)



Other Predictors of TTTS

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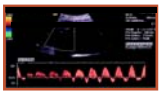
Nuchal Translucency

Folding Intertwin Membrane

Arterio-arterial anastomoses



*Sueters M et al Ultrasound Obstet Gynecol. 2006 Oct;28(5):659-64

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Twin to twin Transfusion Syndrome: Treatment

TTTS: Treatment Options

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- Observation
- Amnioreduction
  - Serial amnioreduction/drainage
  - Amnioreduction with septostomy
- Termination
  - Selective
  - Total
- Laser surgery
- Delivery

TTTS Treatment: Amnioreduction-Septostomy

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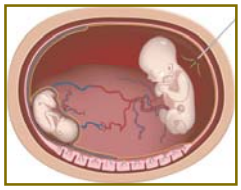

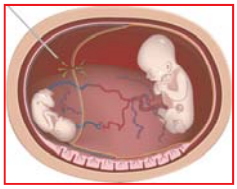

- Palliative treatments
- Survival 51 – 60%
- Neurologic compromise 25-30% - "placental steal"

Moise KJ, Jr.et al. Am J Obstet Gynceol 2005;193:701-7.

TTTS Treatment: Amnioreduction-Septostomy

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Amnioreduction and microseptostomy reduce the efficacy of definitive therapy

Complication	Risk
Iatrogenic membrane separation	9%
Septostomy	10-25%
Discolored or bloody amniotic fluid	> 25%

Quintero RA et al Ultrasound Obstet Gynecol 2005
O' Donoghue K, et al Ultrasound Obstet Gynecol 2007
Leke et al, Prenat Diagn, 2010

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

- Improved survival and decreased neurologic injury with laser as compared to amnioreduction/septostomy

Senat NEJM 04'

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Laser vs Amnioreduction

Outcome	Relative Risk (95% CI)
Dual Death	0.33 (0.16-0.67)
Overall Death	0.71 (0.55-0.92)
Less Perinatal Death	0.59 (0.40-0.87)
Neonatal Death	0.29 (0.14-0.61)
Neurologically intact at 6 months	1.66 (1.17-2.35)

The Cochrane Collaboration 2008

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Laser Surgery:

Indications

- MCDA gestations with Diagnosis of Stage II-IV TTTS
  - Stage I
    - malignant polyhydramnios
    - short cervix
  - If < 18 wks; delay Stage II until 18 weeks if possible

Contraindications

- "short" cervix
- PPROM
- Membrane separation
- Hemorrhage
- Labor

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Stage I TTTS: Laser Surgery vs Observation/Amnioreduction

Case Series	N	Both Survive	One Survive	ALOS	Overall Survival
Huber, 2006	29	76%	17%	93%	84%
Middeldorp, 2007	10	90%	10%	100%	95%
Total	39	79%	15%	94%	87%
Obs/AR Bebbington, 2010	42	70%	22%	92%	82%
Wagner, 2009	30	77%	20%	97%	87%
Total	72	76%	15%	91%	84%

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Laser surgery outside of 16 – 26 week window

Fetoscopic Laser Therapy for Twin–Twin Transfusion Syndrome: Beyond Current Gestational Age Limits

David Baud, MD, PhD[1,2] Rory Windrim, MB[1] Johannes Keunen, MD,PhD,[1] Greg Ryan, MB[1]

[1] Fetal Medicine Unit, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[2] Swiss Laser Group, University Hospitals of Lausanne and Inselspital-Bern, Switzerland

Address for correspondence Greg Ryan, MB, Fetal Medicine Unit, Mount Sinai Hospital, OPG 3-906, 600 University Avenue, Toronto, ON M5G 1X5, Canada (e-mail: gryan@mtsinai.on.ca).

Am J Perinatol 2014;31:519–524.

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Laser surgery outside of 16 – 26 week window

Early Laser (2.5%)

- Similar outcomes to cases done between 16 -26 weeks
- Increased incidence of PPROM
- Different diagnostic criteria

Baud et al 2013

Late Laser (4-8%)

- Amnioreduction increases risk of "placental steal" (Rodeck 2006)
- Compared to amnioreduction, late laser demonstrates;
  - Increased gestational length 31 vs 9 days (p=0.07)
  - Decreased neonatal morbidity 0 vs 27% (p=0.02)
  - Lower neonatal death rate 0 vs 14%

Middeldorp et al 2007

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Fetoscopic Laser Photocoagulation

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TTTS treatment: Laser Surgery

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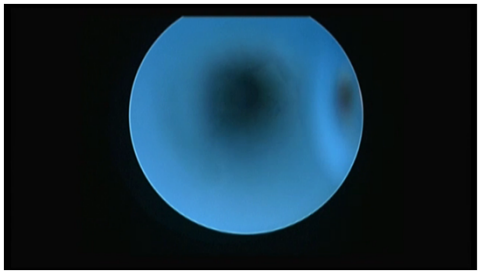
TTTS treatment: Laser Surgery



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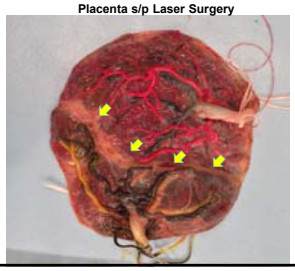
TTTS treatment: Laser Surgery

Non-TTTS Monochorionic Placenta

- **TTTS/IUGR Monochorionic Placenta s/p Laser Surgery**



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Laser surgery TTTS: Solomonization

Outcome	Solomon Group (234 fetuses)	Standard Laser (270 fetuses)	CI
Overall Survival	74%	73%	NS
ALOS	85%	87%	NS
Dual Survival	64%	60%	NS
TAPS	3%	16%	0.16 (0.05-0.49)
Recurrent TTTS	1%	7%	0.21 (0.04-0.98)
Neuro Morbidity	8%	13%	NS

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Laser Surgery: Complications

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Laser Surgery: Complications

- Maternal
  - Bleeding
  - Infection
- Fetal
  - Demise
  - PPROM
  - Preterm Birth
- Operative
  - Recurrent TTTS/TAPS

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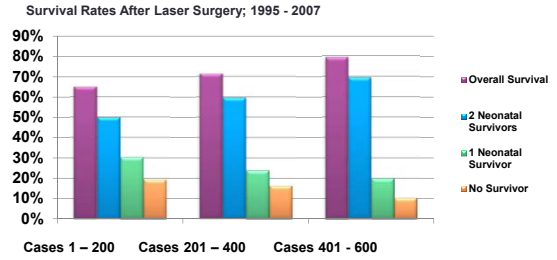
Laser Surgery Complications: Fetal Demise



Diehl et al 2014

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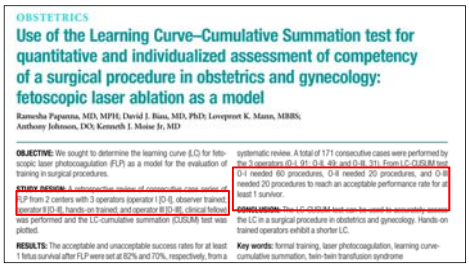
Laser Surgery TTTS: Outcomes



OBSTETRICS

Use of the Learning Curve–Cumulative Summation test for quantitative and individualized assessment of competency of a surgical procedure in obstetrics and gynecology: fetoscopic laser ablation as a model

Ramesha Papanna, MD, MPH; David J. Biau, MD, PhD; Lovepreet K. Mann, MBBS; Anthony Johnson, DO; Kenneth J. Moise Jr, MD

OBJECTIVE: We sought to determine the learning curve (LC) for fetoscopic laser photocoagulation (FLP) as a model for the evaluation of training in surgical procedures.

STUDY DESIGN: A retrospective review of consecutive case series of FLP from 2 centers with 3 operators (operator I [O-I], observer trained; operator II [O-II], hands-on trained; and operator III [O-III], clinical fellow) was performed and the LC-cumulative summation (CUSUM) test was plotted.

systematic review. A total of 171 consecutive cases were performed by the 3 operators (O-I, 91; O-II, 49; and O-III, 31). From LC-CUSUM test, O-I needed 60 procedures, O-II needed 20 procedures, and O-III needed 20 procedures to reach an acceptable performance rate for at least 1 survivor.

CONCLUSION: The LC-CUSUM test can be used to successfully assess the LC in a surgical procedure in obstetrics and gynecology. Hands-on trained operators exhibit a shorter LC.

RESULTS: The acceptable and unacceptable success rates for at least 1 fetus survival after FLP were set at 82% and 70%, respectively, from a

Key words: formal training, laser photocoagulation, learning curve-cumulative summation, twin-twin transfusion syndrome

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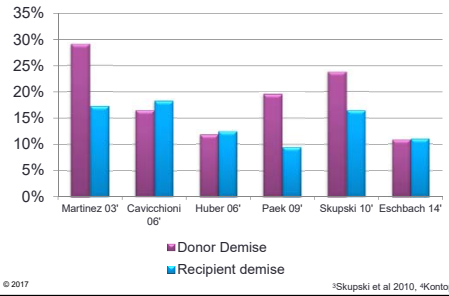
Fetal Demise Rates



Donor demise reported in 13-54% of cases and recipient demise in 9-24% of cases[3,4,5]

[3]Skupski et al 2010, [4]Kontopoulos et al 2007, [5]Nakata et al 2009

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Fetal Demise After Laser Surgery

Original Research

Donor Death After Selective Fetoscopic Laser Surgery for Twin–Twin Transfusion Syndrome

Saul Snowise, MD, Kenneth J. Moise, MD, Anthony Johnson, DO, Michael W. Bebbington, MD, and Ramesha Papanna, MD, MPH

VOL. 126, NO. 1, JULY 2015 OBSTETRICS & GYNECOLOGY

Definition: Loss of cardiac activity prior to onset of labor

15% fetal demise rate (13% donor, 2% recipient)

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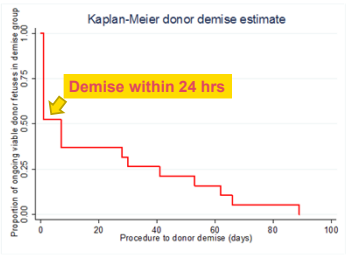
Donor Demise: Procedure to Demise Interval



Median 4 days [1-89]

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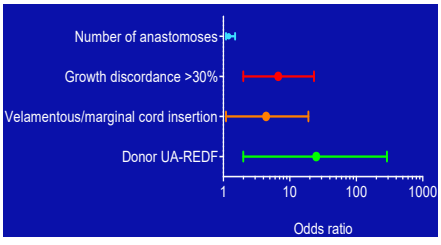
Donor Demise: Multivariate Regression



Snowise et al, 2014

PPROM After Laser Surgery for TTTS

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Ultrasound Obstet Gynecol 2017; 49: 607–611
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.15958

Preterm prelabor rupture of membranes after fetoscopic laser surgery for twin–twin transfusion syndrome

S. SNOWISE, L. K. MANN, K. J. MOISE JR, A. JOHNSON, M. W. BEBBINGTON and R. PAPANNA

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology and Reproductive Sciences, UT Health-University of Texas Medical School at Houston and The Fetal Center at Children's Memorial Hermann Hospital, Houston, TX, USA

Definition: Rupture of membranes after laser surgery and before 34 weeks gestation

Incidence: 41%

PPROM After Laser Surgery for TTTS

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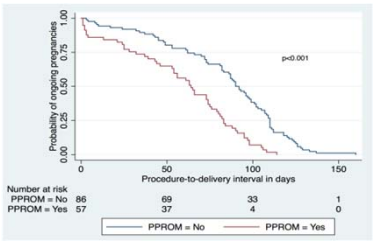

Latency of Labor After PPROM by Gestational Age

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Gestational age at PPROM (weeks)	Number	PPROM to Delivery (days) Median[range]
< 24	16	1[0-93]
24 – 27^6	12	18.5[0-57]
28-31^6	20	0[0-21]
32+	12	1[0-6]

PPROM After Laser Surgery for TTTS

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PPROM After FLS for TTTS	No PPROM n=92	PPROM n=64	P-value/ OR (95% CI)
Gestational Age at Delivery (weeks)	32.8±3.9	29.1±4.4	<0.01
Overall Survival	89%	79%	0.016

•PPROM increases Prematurity (decreases gestational length) by 3.7 weeks and decreases overall survival

Snowise et al, 2016

TTTS Fetosocpy Outcomes: June 2017 – October 2018

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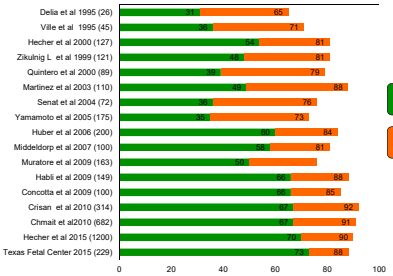
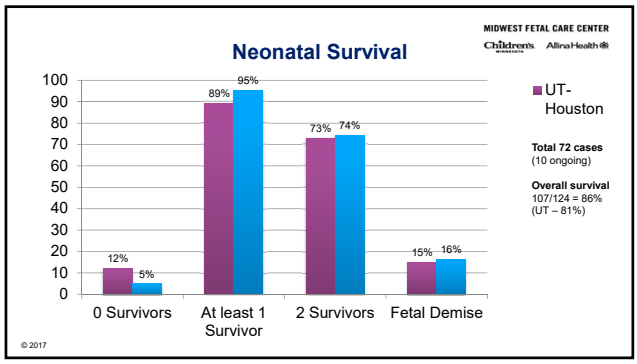
Laser Surgery TTTS: Outcomes

MIDWEST FETAL CARE CENTER




MIDWEST FETAL CARE CENTER
Neonatal Survival
100
90
80
70
60
50
40
30
20
10
0
12%
5%
89%
95%
73%
74%
15%
16%
0 Survivors
At least 1 Survivor
2 Survivors
Fetal Demise
UT-Houston
Total 72 cases
(10 ongoing)
Overall survival
107/124 = 86%
(UT – 81%)
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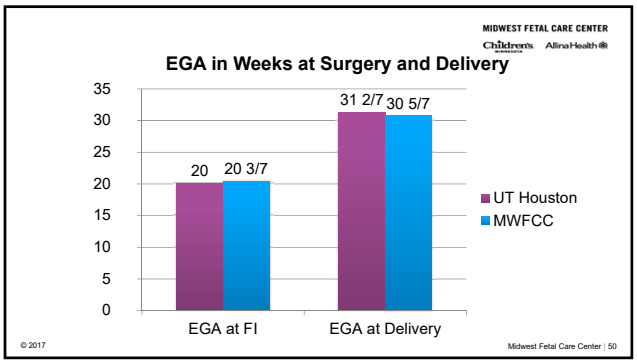
MIDWEST FETAL CARE CENTER
EGA in Weeks at Surgery and Delivery
35
30
25
20
15
10
5
0
20
20 3/7
31 2/7
30 5/7
EGA at FI
EGA at Delivery
UT Houston
MWFCC
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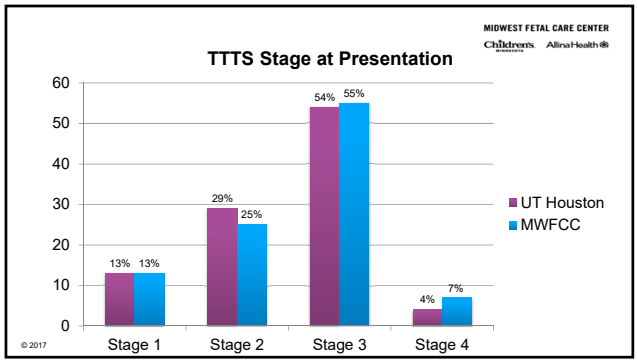
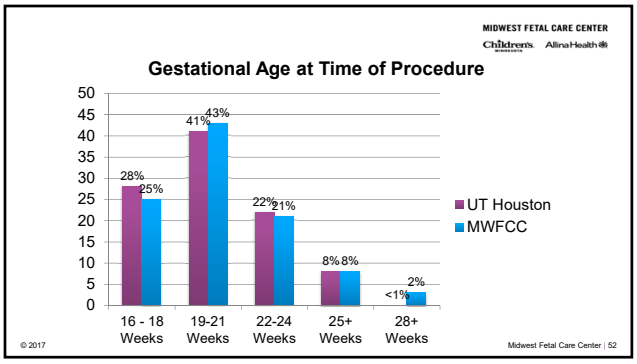
Midwest Fetal Care Center | 50


MIDWEST FETAL CARE CENTER
TTTS Stage at Presentation
60
50
40
30
20
10
0
13%
13%
29%
25%
54%
55%
4%
7%
Stage 1
Stage 2
Stage 3
Stage 4
UT Houston
MWFCC
© 2017


MIDWEST FETAL CARE CENTER
Gestational Age at Time of Procedure
50
45
40
35
30
25
20
15
10
5
0
28%
25%
41%
43%
22%
21%
8%
8%
2%
<1%
16 - 18 Weeks
19-21 Weeks
22-24 Weeks
25+ Weeks
28+ Weeks
UT Houston
MWFCC
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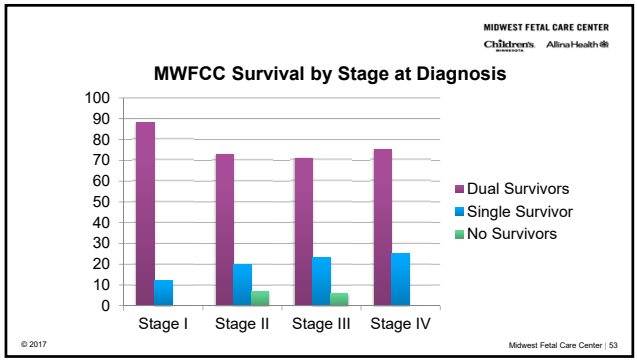
Midwest Fetal Care Center | 52


MIDWEST FETAL CARE CENTER
MWFCC Survival by Stage at Diagnosis
100
90
80
70
60
50
40
30
20
10
0
Stage I
Stage II
Stage III
Stage IV
Dual Survivors
Single Survivor
No Survivors
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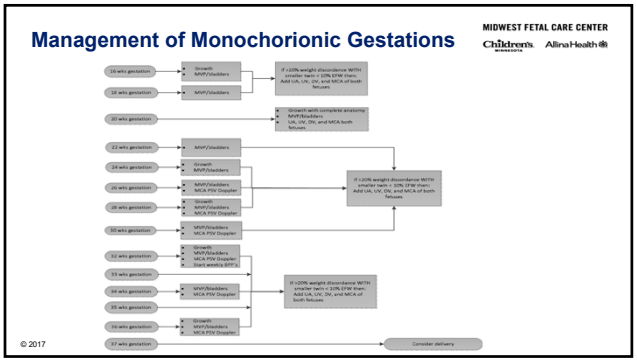
Midwest Fetal Care Center | 53


Management of Monochorionic Gestations
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Children's MINNESOTA Allina Health

Other Outcomes

1. Incomplete lasers n=2
2. Septostomy n=7
   - 4 unintentional
   - 3 intentional
3. Repeat cases (TAPS/recurrent TTTS) n=0
4. Maternal abruption n=3
5. Maternal infections n=0
6. Triplets n=2
7. Laparoscopic assisted cases n=5
8. Mini-laparotomy cases n=5

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Children's MINNESOTA Allina Health

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Children's MINNESOTA Allina Health

TTTS: "Other" Staging Criteria

Abnormal Cardiac Findings in Stage I Recipient Twins

Cardiac finding	%
Ventricular hypertrophy	57
Atrioventricular valve regurgitation	14
Moderate to severe TR	7
Ventricular systolic dysfunction	21
Cardiomegaly	7
Elevated RV-MPI	30
Elevated LV-MPI	55

Michelfelder E, et al, 2007

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Children's MINNESOTA Allina Health

PPROM After Laser Surgery for TTTS

PPROM Incidence	41% (n=64)
PPROM Gestational Age	27.4±5 weeks
PPROM-to-Delivery Interval	Median = 1 day [interquartile range 0-13 days]
Procedure-to-Delivery Interval	43.8±32 weeks