The University of Texas at Austin

Women's Health

Dell Medical School

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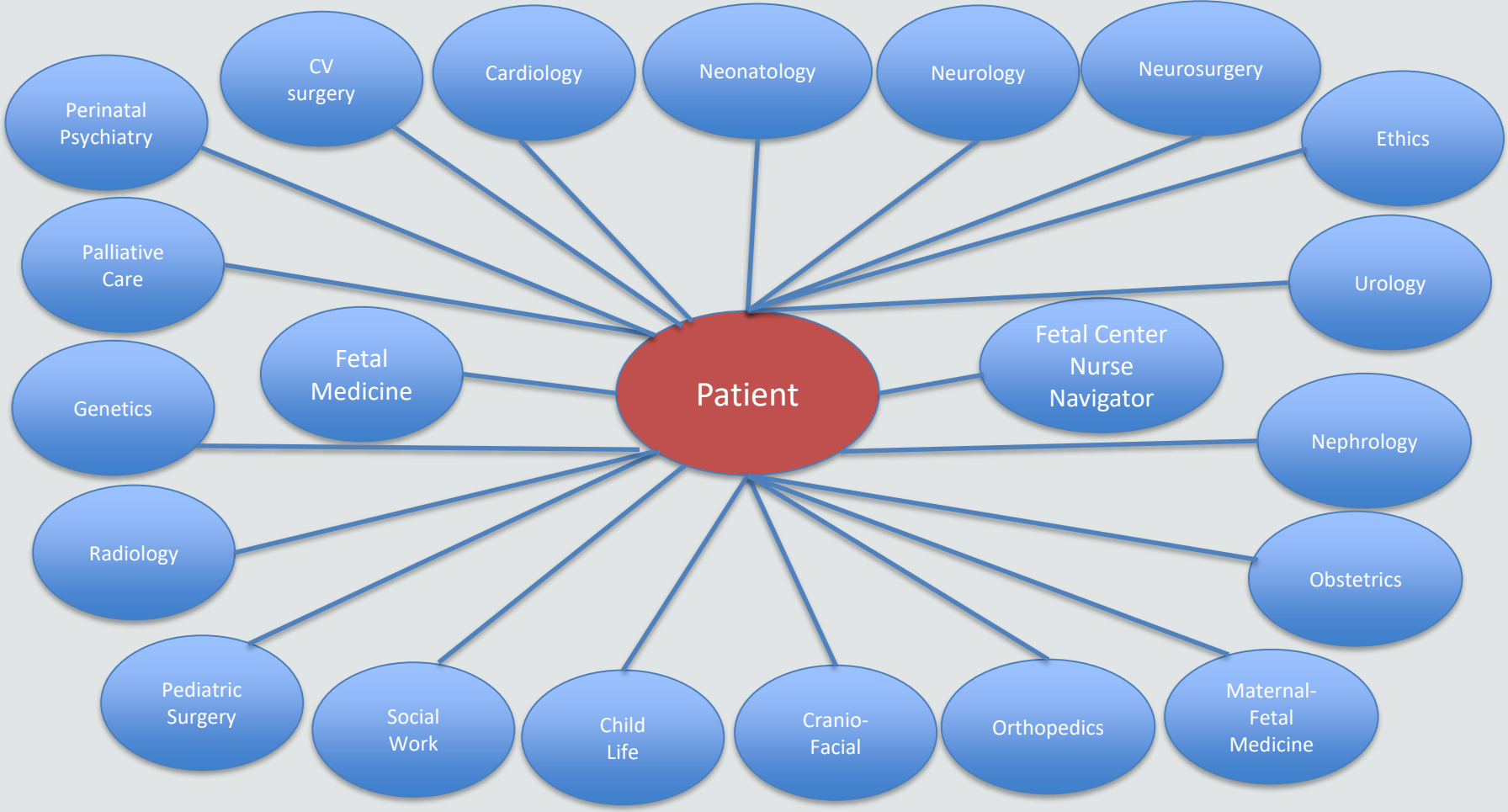
Director, Comprehensive Fetal Care Center
Dell Children's Hospital

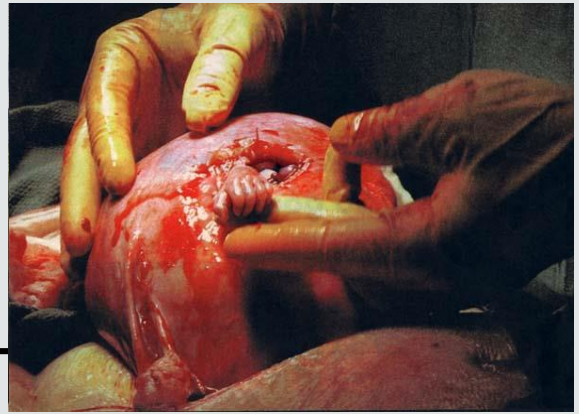
Disclaimers

- Consultant: Jansen Pharmaceuticals (Division of Johnson and Johnson)
- Research support: Jansen Pharmaceuticals (Division of Johnson and Johnson)
- Royalties for chapter authorship: UpToDate, Inc.


Patient
Perinatal Psychiatry
CV surgery
Cardiology
Neonatology
Neurology
Neurosurgery
Ethics
Palliative Care
Urology
Fetal Medicine
Fetal Center Nurse Navigator
Genetics
Nephrology
Radiology
Obstetrics
Pediatric Surgery
Social Work
Child Life
Cranio-Facial
Orthopedics
Maternal-Fetal Medicine

North American Fetal Treatment Network

Definition of Maternal-Fetal Surgery



- Operating on two patients simultaneously where both incur risks
- Benefits to mother probably not medically definable
- Opportunity to correct a surgically-treatable lesion or diminish its sequelae

Evidenced Based Surgical Therapies

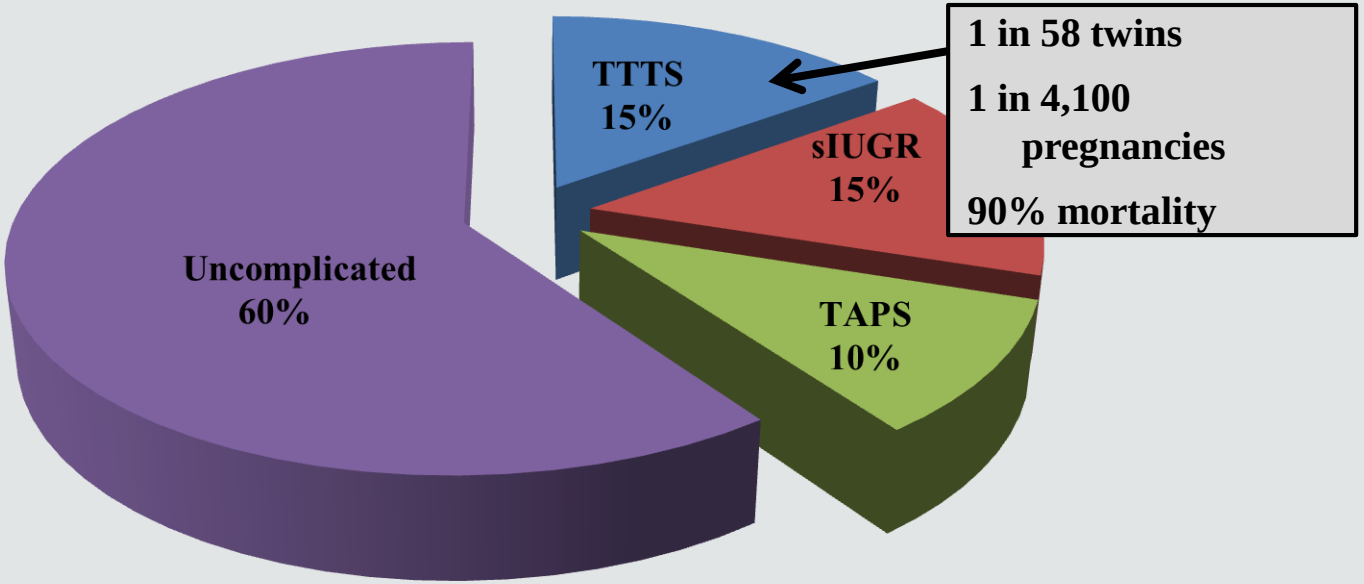
- 1963: Intraperitoneal transfusion for severe fetal anemia due to Rh disease; intravascular transfusion (1982)
- 1982: Vesicoamniotic shunt for lower urinary tract obstruction

<u>THEN</u>

- 2004: Laser for severe twin-twin transfusion syndrome
- 2011: Open maternal-fetal surgery for spina bifida repair
- 2021: Tracheal occlusion for fetal diaphragmatic hernia

Twin – Twin Transfusion Syndrome

Monochorionic Twins
Complications



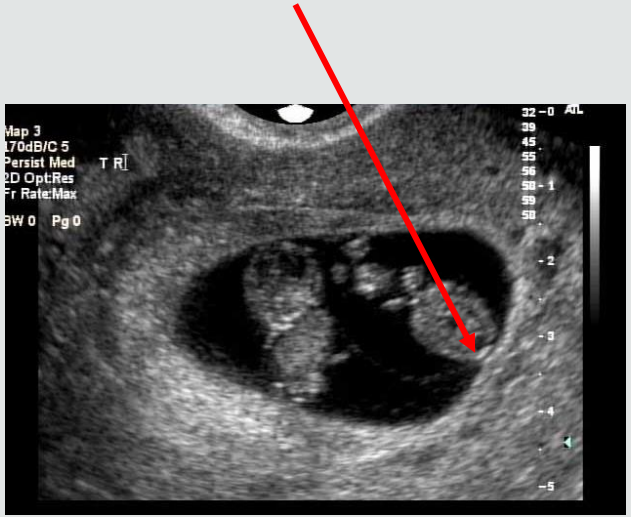
Society for Maternal-Fetal Medicine Guidelines for Monochorionic Twins

- Determine chorionicity at 10 – 13 weeks gestation
- Follow MVP's and bladders Q 2 weeks starting at 16 weeks gestation
- Follow growth every 4 weeks
- Dopplers? – UA only for IUGR

SMFM, Simpson L. Am J Obstet Gynecology 2013;208: 3-18.

Multifetal Pregnancies
Establish Chorionicity @ 10-14 Weeks

- **“T” sign**
- **Monochorionic**



- **Twin Peak (lambda)**
- **Dichorionc**

Monochorionic Twins/ TTTS Staging

Stage 1

Donor MVP <2 cm;

Recipient MVP >8-10 cm

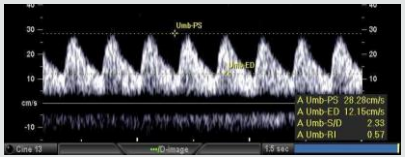
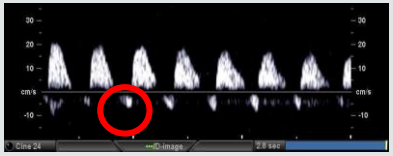
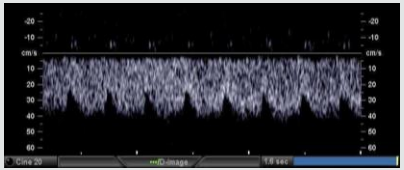
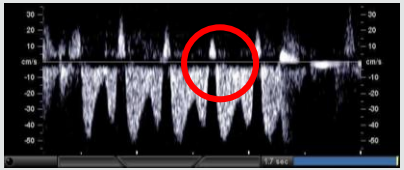
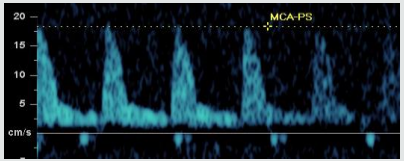
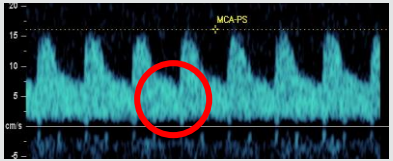
Stage 2

Absent bladder in donor twin;

normal Doppler studies

Monochorionic Twins/TTTS Staging

Stage 3

	Normal	Abnormal	
Umbilical Artery			Donor
Umbilical Vein			Recipient
Ductus Venosus			
Middle Cerebral Artery			

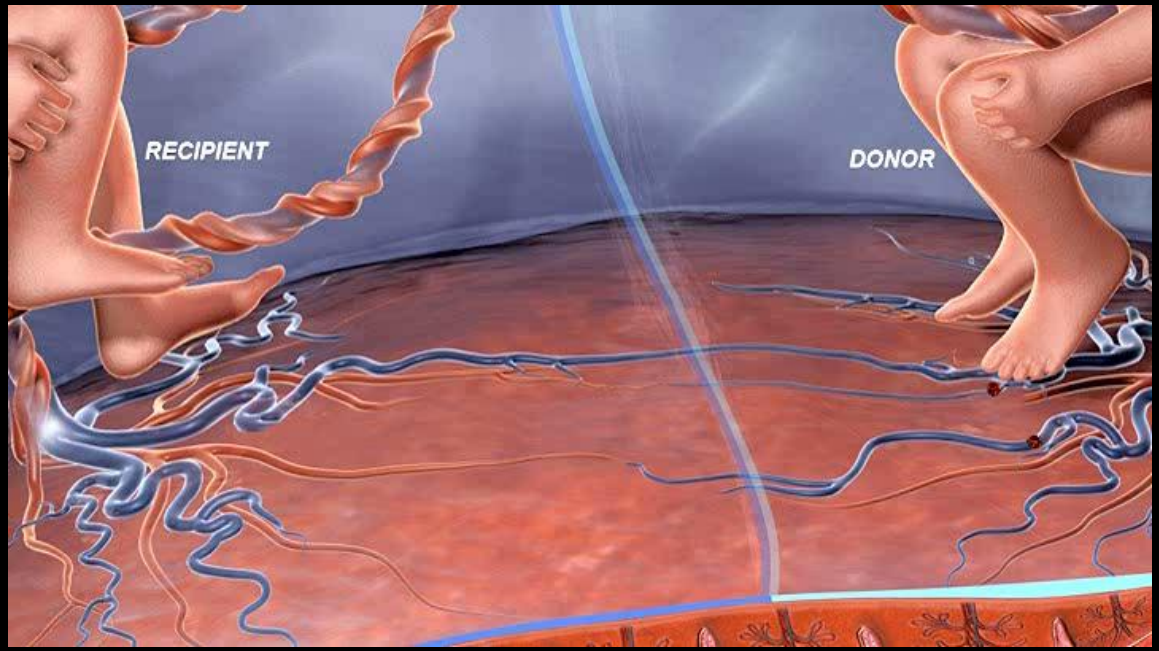
Monochorionic Twins/TTTS Staging

Stage 4

Stage 5

One or both fetuses have died

Monochorionic Twins/ Pathophysiology of TTTS

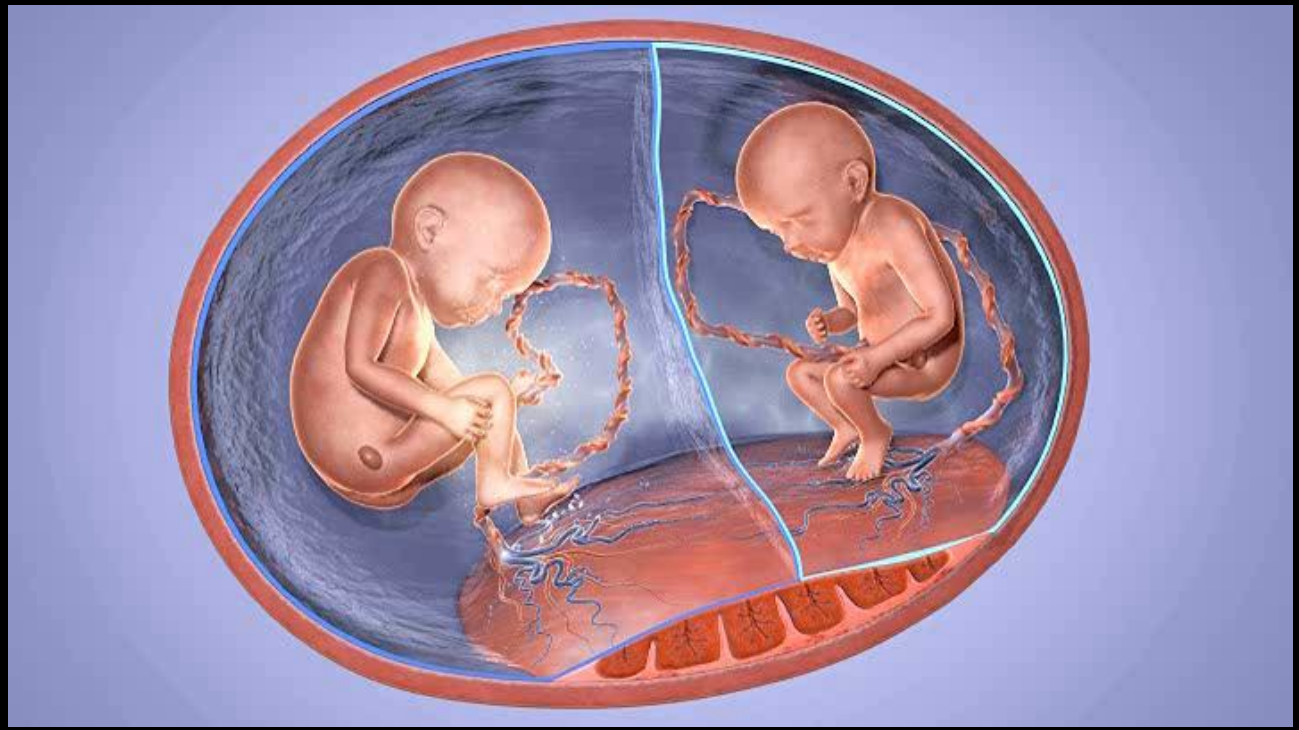


Monochorionic Twins
Laser vs. Amnio for TTTS

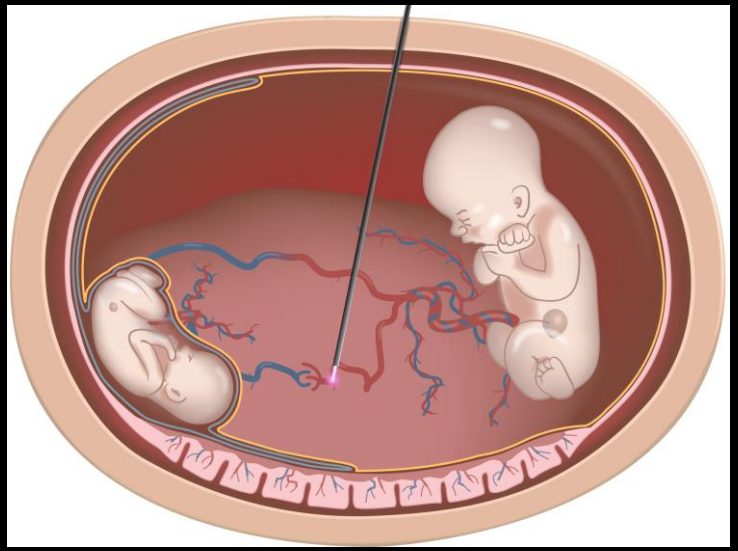
	Laser	Amnioreduction
Survival of one fetus	40%	26%
Survival of both fetuses	36%	26%
Survival of at least one fetus	76%	51%
GA at delivery	33.3	29.0
Alive w/o neurologic problems	52%	31%

Senat et al. N Eng J Med 2004; 351:136-44

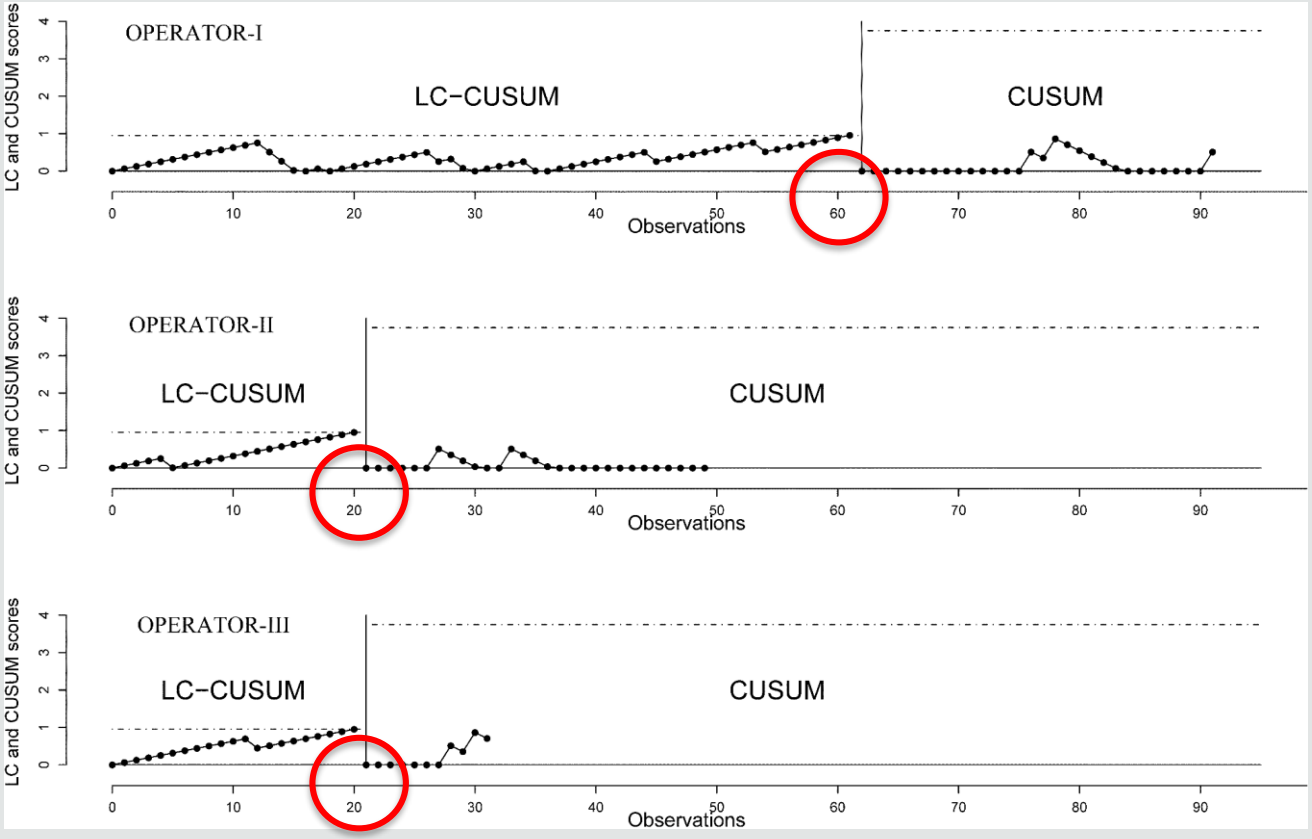
Laser Photocoagulation



Laser Photocoagulation for Twin-Twin Transfusion



Learning Curve for Laser



Papanna et al.
Am J Obstet Gynecol 2011; 204:218e1-9

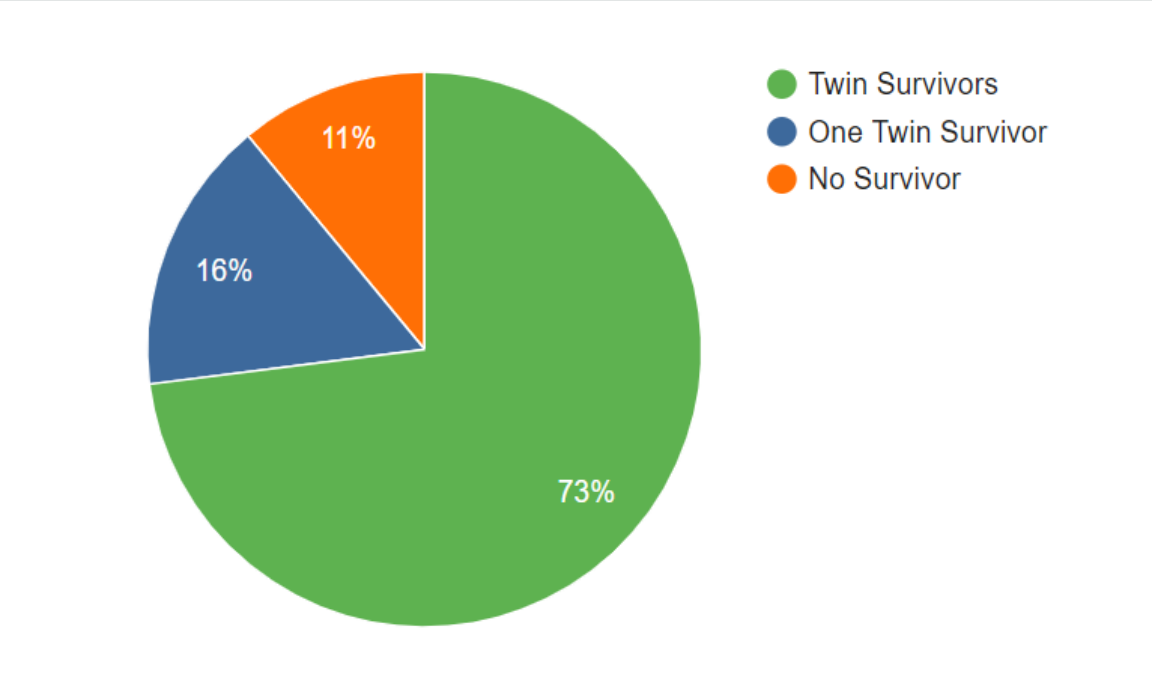
Learning Curve for Laser

	Cohort 2000-2005 N=153	Cohort 2008-2010 N=165
Neurodevelopmental Impairment	**28 (18%)**	**10 (6%)**
Cognitive Impairment	6 (4%)	3(2%)
Motor Impairment	6(4%)	1(1%)
Cerebral Palsy	1(1%)	2(1%)
CP+cognitive+motor	4(3%)	1(1%)
CP+cognitive	1(1%)	0
CP+motor	5(3%)	2(1%)
CP + deafness	1(1%)	0
Cognitive + Motor	3(2%)	1(1%)
Cognitive+Motor+deafness	1(1%)	0

Van Klink et al. Am J Obstet Gynecol 2014;210:540.e1-7

Laser Photocoagulation Outcome

420 cases with neonatal survival to 30 days of life



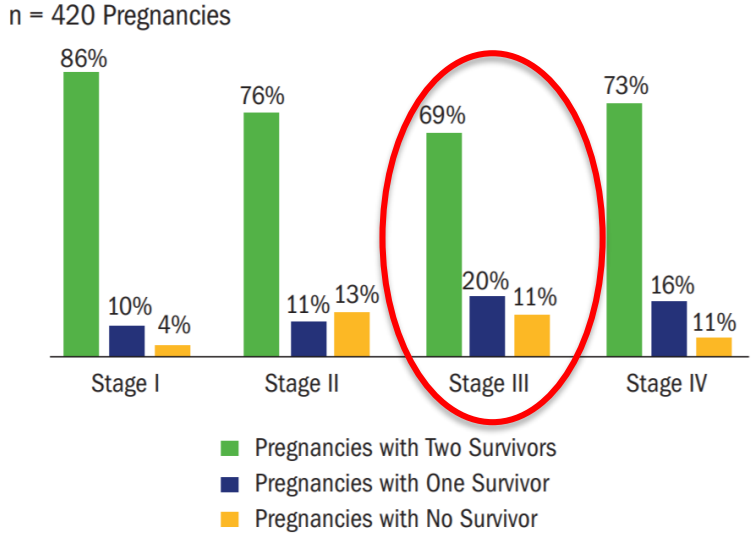
Laser Photocoagulation Outcome

Survival Rate at 30 Days Post-Delivery

30-Day Post-Delivery Survival Rate by Gestational Age at Time of Fetal Intervention

Gestational Age at Time of Procedure	Total	Pregnancies with Two Survivors	Pregnancies with One Survivor	Pregnancies with No Survivors
16 – 18 weeks	124	85 (69%)	25 (20%)	14 (11%)
19 – 21 weeks	174	134 (77%)	16 (9%)	24 (14%)
22 – 24 weeks	85	62 (73%)	16 (19%)	7 (8%)
25 – 27 weeks	35	26 (74%)	9 (26%)	0 –
28+ weeks	2	1 (50%)	1 (50%)	0 –
SUMMARY	**420**	**308 (73%)**	**67 (16%)**	**45 (11%)**

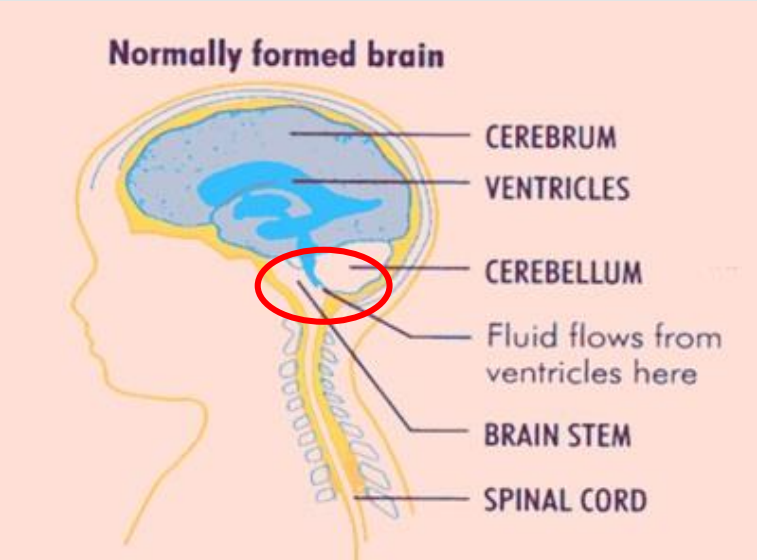
30-Day Post-Delivery Survival Rate by TTTS Stage

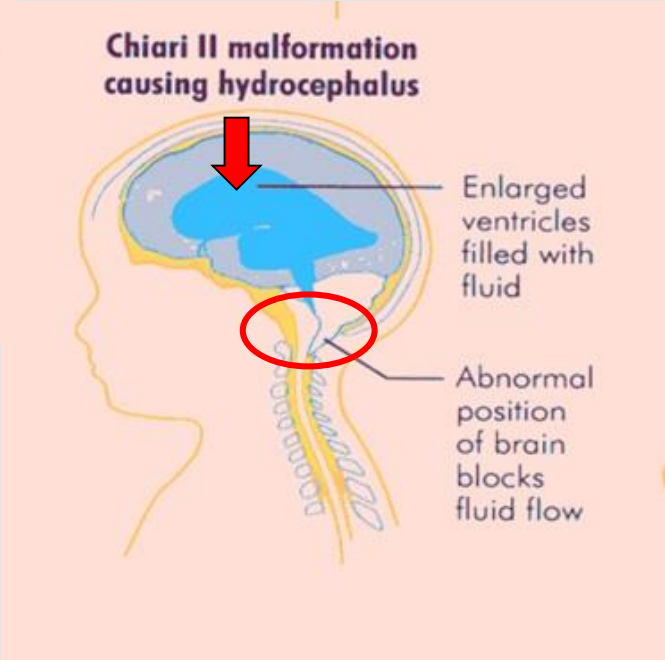


Myelomeningocoele

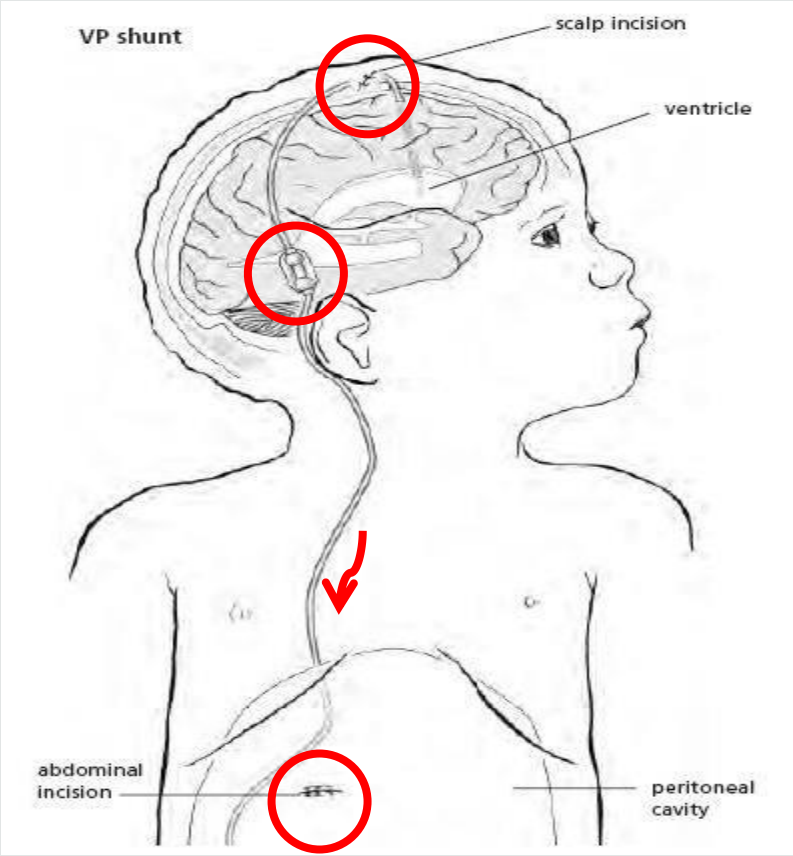
The Impact of Spina Bifida

- 1500 children born in U.S. annually/ 200 in Texas alone
- Lifetime medical costs: $500,000 – $1 million


Normally formed brain
CEREBRUM
VENTRICLES
CEREBELLUM
Fluid flows from ventricles here
BRAIN STEM
SPINAL CORD

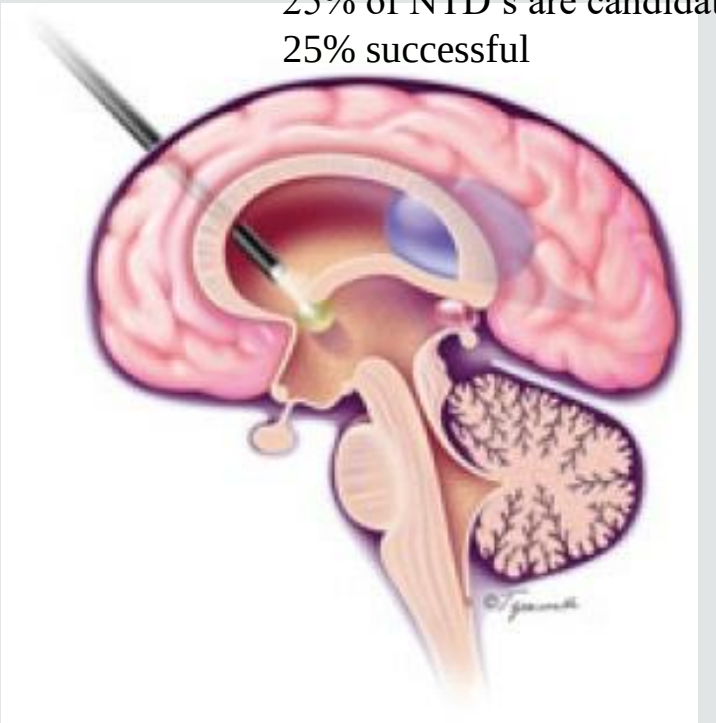

Chiari II malformation causing hydrocephalus
Enlarged ventricles filled with fluid
Abnormal position of brain blocks fluid flow

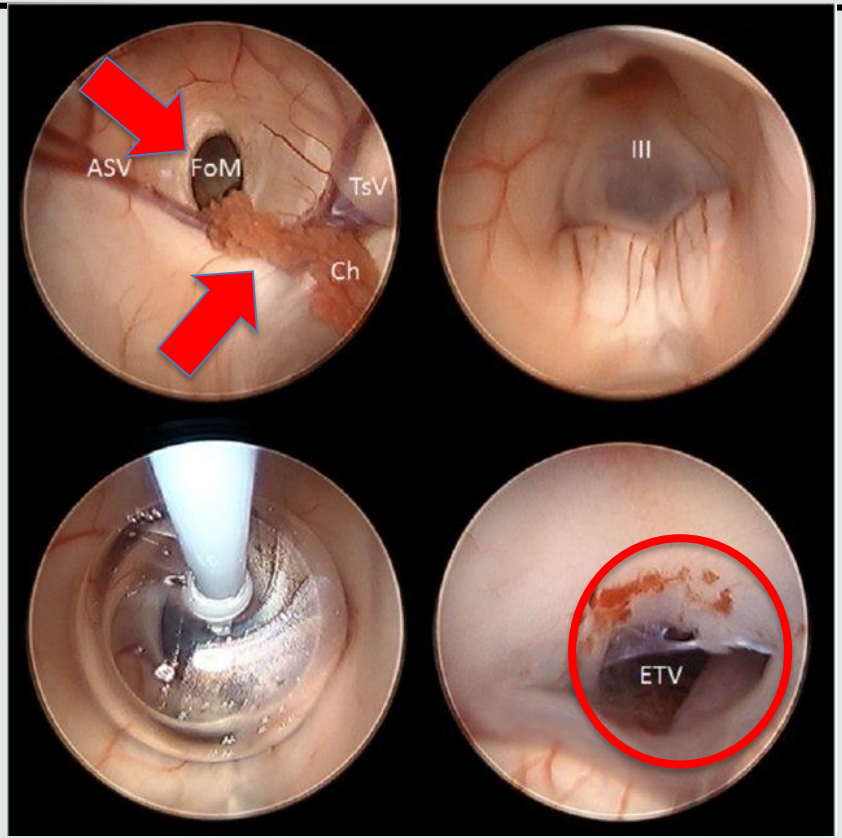
Hindbrain Herniation


VP shunt
scalp incision
ventricle
abdominal incision
peritoneal cavity

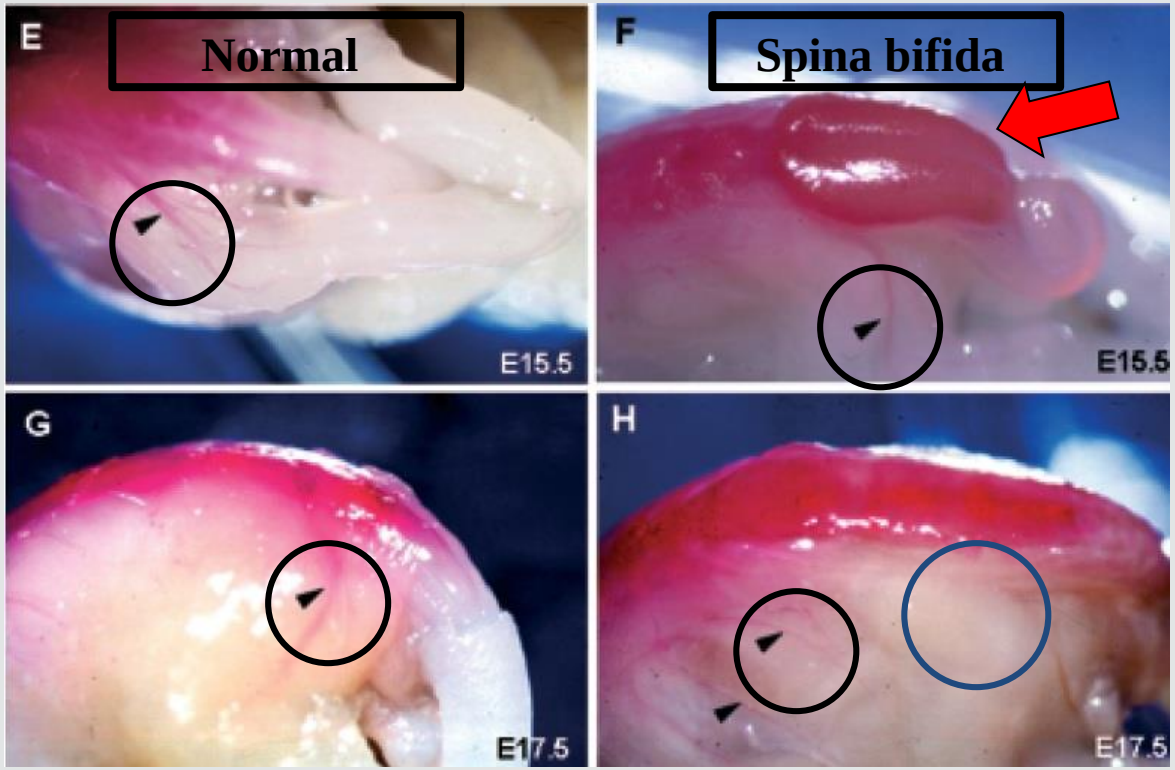
Endoscopic Third Ventriculostomy (ETV)

25% of NTD's are candidates
25% successful





Mouse model



Stiefel et al. J Neurosurg 2007;106:213-21

Feb 2003 – Dec 2010

$22.5 million

MOMS Outcomes (Neonatal)

Outcome	Fetal surgery	Postnatal surgery
Gest Age (wks)	34.1 ± 3.1	37.3 ± 1.1
< 30 wks	13%	0%
30 – 34 wks	33%	5%
35 – 36 wks	33%	8%
Birthweight (gms)	2383 ± 688	3039 ± 469
Respiratory distress syndrome	21%	6%

1 in 5 delivered at term

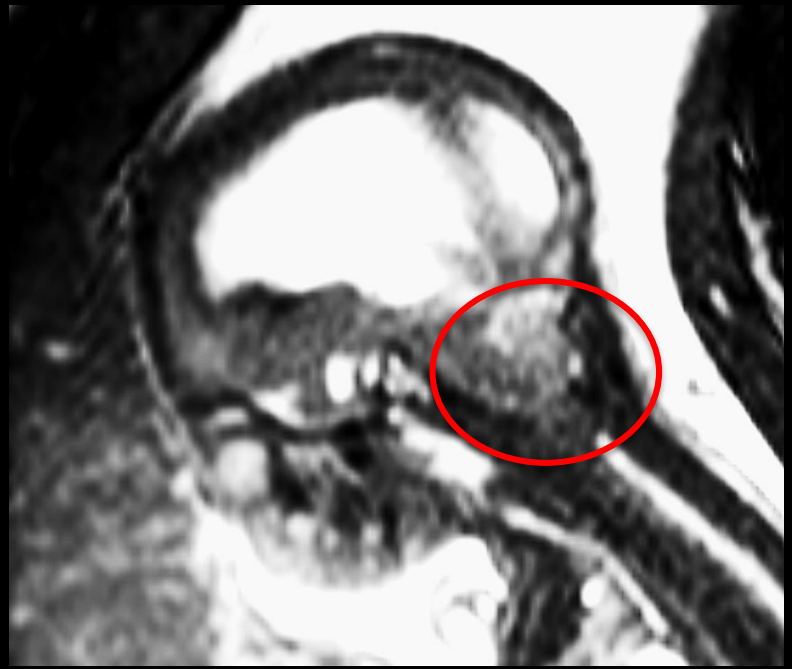
Adzick et al. N Eng J Med 2011;364;993-1004

MOMS Outcomes (Pediatric)

Outcome	Fetal surgery		Postnatal surgery		P value
	Initial	MOMS2	Initial	MOMS2	
Death	2	5	0	3	
Shunt placement	40%	49%	82%	85%	< 0.001 <0.001
Shunt revision		23%		60%	< 0.001
Any hindbrain herniation	64%	61%	96%	87%	< 0.001 < 0.001
Tethered cord release	8%	27%	1%	15%	0.06 0.03
Chiari decompression	1%	4%	5%	11%	0.37 0.15
Epidermoid cysts	3%	11%		3%	1.00 0.17

Adzick et al. N Eng J Med 2011;364;993-1004/ Houtrow et al. Pediatrics 2020;145:e20191544

Reversal of Chiari II



MOMS Pediatric Outcomes

Outcome	Fetal surgery		Postnatal surgery		P value
	MOMS	MOMS 2	MOMS	MOMS 2	
Bayley MDI	89.7		87.3		0.53
KBIT-2	99.0		91.6		0.05
Δ motor/anat level > 2 levels higher	32%		12%		0.02
Walking independently	42%	29%	21%	11%	0.03 < 0.001

Adzick et al. N Eng J Med 2011;364;993-1004
Houtrow et al. Pediatrics 2020;145:e20191544

Pre-operative Counseling

Will prenatal surgery affect ambulation?

(30 month study of entire MOMS cohort)

Parameter	Walking independently	Not walking independently	P value
No knee movement	8%	92%	0.17
No hip movement	11%	89%	0.43
No clubfoot	33%	67%	0.02
L3-S1 lesion	21%	79%	0.10
Third ventricle dilation	27%	83%	0.37
Sac over lesion	18%	82%	0.004

Logistic regression: Lower than L3 lesion, third ventricle dilation and myeloschisis associated independent ambulation

Farmer et al. Am J Obstet Gynecol 2018;218:256 e1-13

Pre-operative Counseling

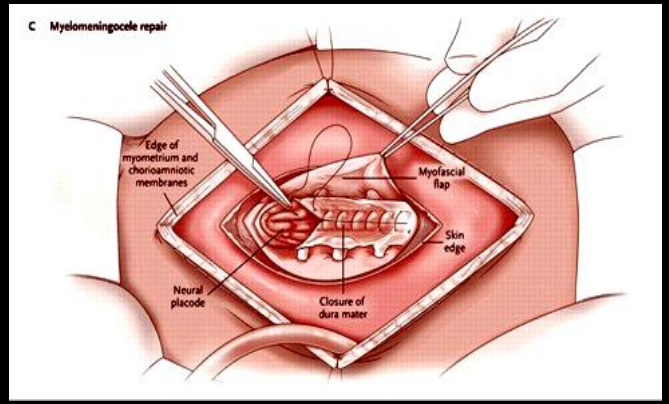
Will prenatal surgery affect the need for a VP shunt?

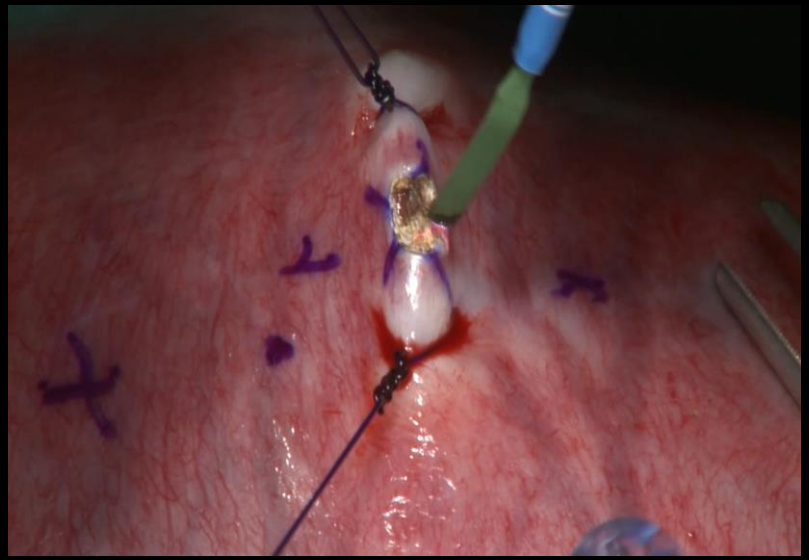
(Data based on prenatal US assessment)

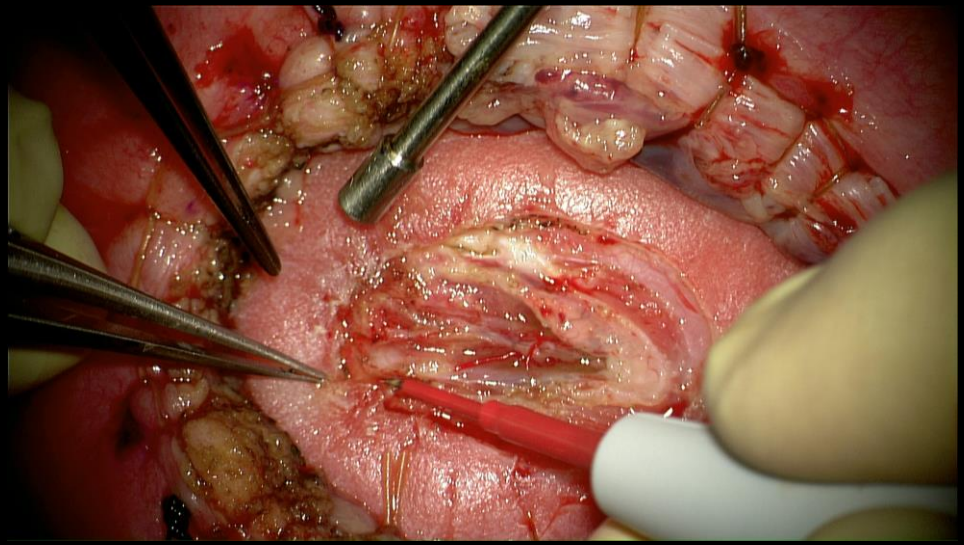
Vent size	Prenatal repair	Post-natal repair	P value
< 10 mm	20%	79%	0.01
10 – 15 mm	45%	86%	
≥ 15 mm	79%	88%	

Tuilpan et al. J Neurosurg Pediatr 2015; 16:613-20

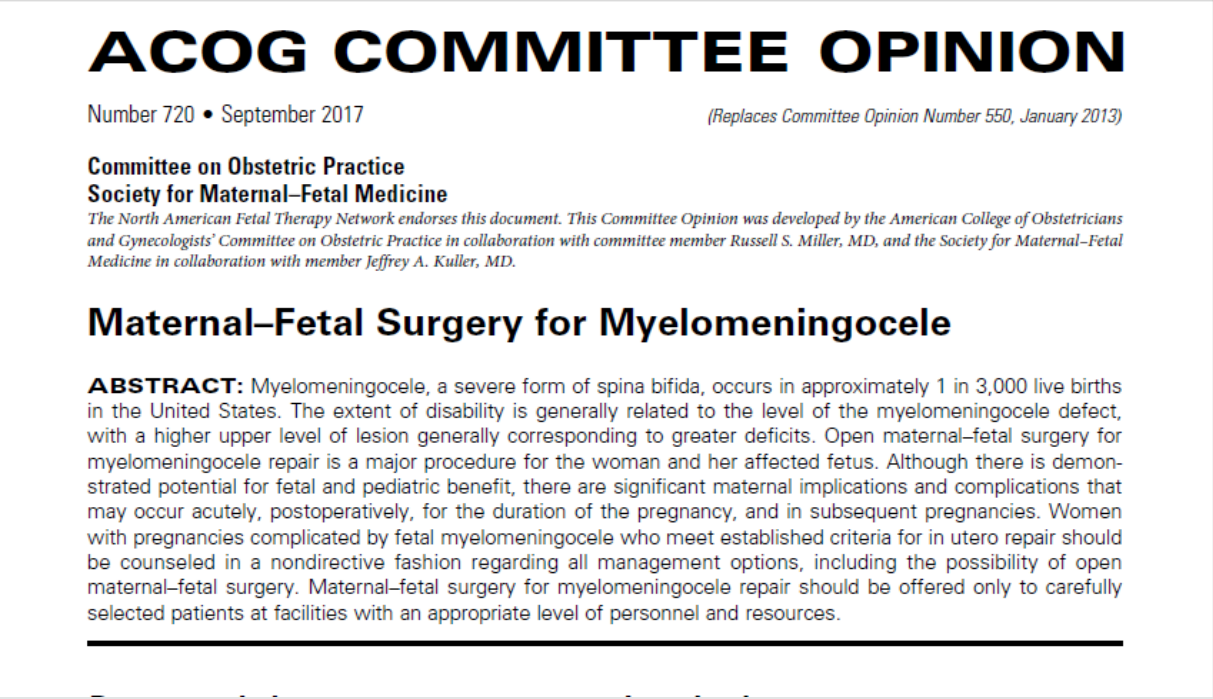
Open Fetal Myelomeningocele Repair







Open NTD Surgery



ACOG COMMITTEE OPINION

Number 720 • September 2017 *(Replaces Committee Opinion Number 550, January 2013)*

Committee on Obstetric Practice
Society for Maternal–Fetal Medicine

The North American Fetal Therapy Network endorses this document. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee member Russell S. Miller, MD, and the Society for Maternal–Fetal Medicine in collaboration with member Jeffrey A. Kuller, MD.

Maternal–Fetal Surgery for Myelomeningocele

ABSTRACT: Myelomeningocele, a severe form of spina bifida, occurs in approximately 1 in 3,000 live births in the United States. The extent of disability is generally related to the level of the myelomeningocele defect, with a higher upper level of lesion generally corresponding to greater deficits. Open maternal–fetal surgery for myelomeningocele repair is a major procedure for the woman and her affected fetus. Although there is demonstrated potential for fetal and pediatric benefit, there are significant maternal implications and complications that may occur acutely, postoperatively, for the duration of the pregnancy, and in subsequent pregnancies. Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in a nondirective fashion regarding all management options, including the possibility of open maternal–fetal surgery. Maternal–fetal surgery for myelomeningocele repair should be offered only to carefully selected patients at facilities with an appropriate level of personnel and resources.

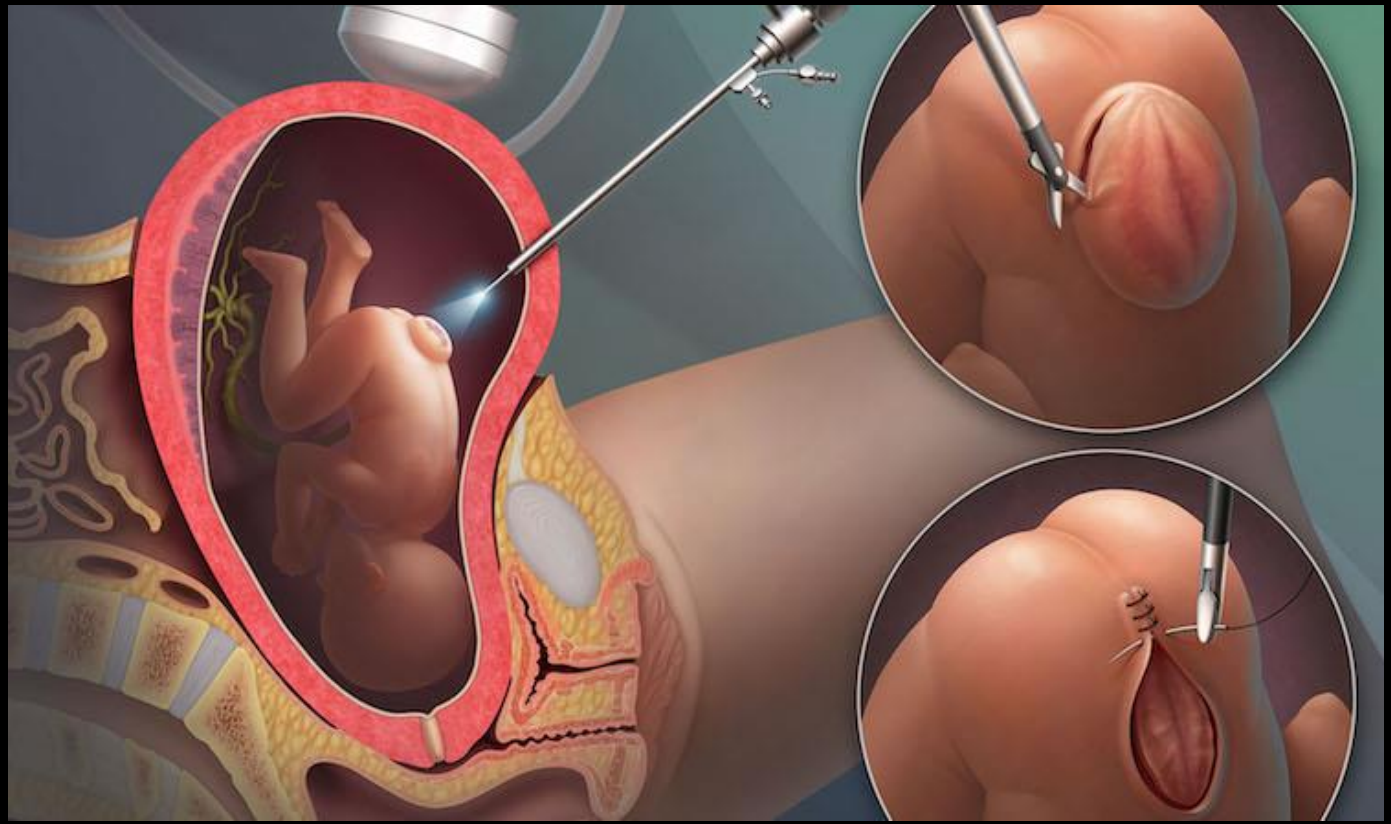
Maternal Outcomes

693 pregnancies in NAFTNet registry

- 77 pregnancies in 60 women
- 5 ruptures (9.6%)
- 2/5 fetal deaths
- Median GA at rupture: 28 wks (26-31.5 wks)
- No predictors
  - ✓ Inter-pregnancy interval
  - ✓ GA at previous fetal surgery
  - ✓ Condition of hysterotomy

Goodnight et al. Am J Obstet Gynecol 2019;220:494.e1-e7

Fetoscopic Spina Bifida Repair



Open vs Fetoscopic MMC Repair

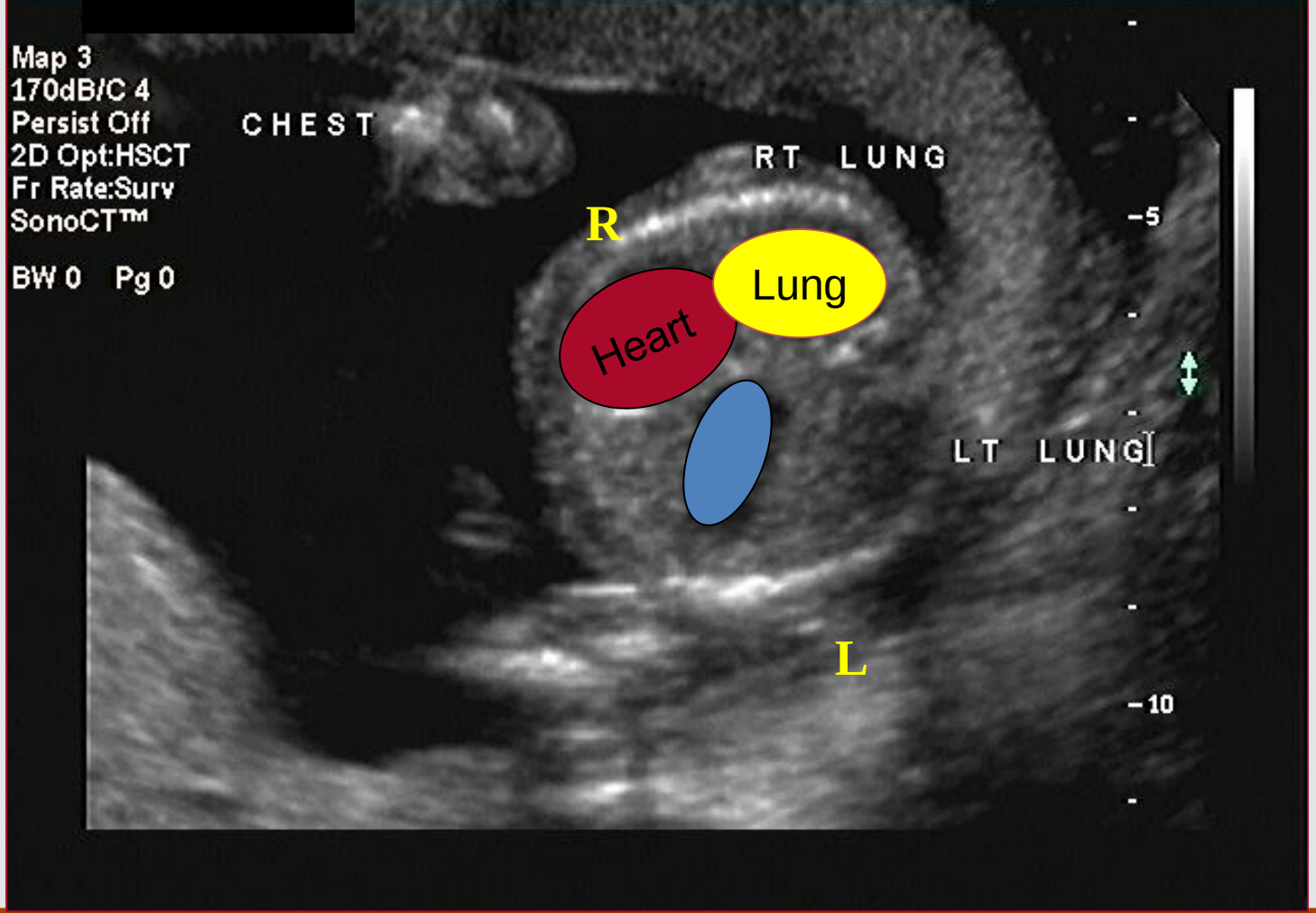
Outcome	Open repair	Fetoscopic Repair	P value
Gest Age @ birth < 30 wks	8%	11%	0.26
Gest Age @ birth < 37 wks	73%	85%	0.38
PPROM	29%	77%	0.07
Perinatal mortality	6%	6%	0.86
Revision of MMC repair	5%	30%	< 0.01
Shunt	34%	44%	0.27
Reversal of Chiari	71%	69%	0.91
Functional vs anatomical level	55%	69%	0.18

Kabagambe et al. Fetal Diagn Ther 2018; 43:161-74

Diaphragmatic Hernia

Epidemiology of Congenital Diaphragmatic Hernia

- 1600 babies born with CDH each year
- 90% left-sided
- 60% are an isolated defect
- 50% overall mortality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Persist Off
2D Opt:HSCT
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BW 0 Pg 0
CHEST
RT LUNG
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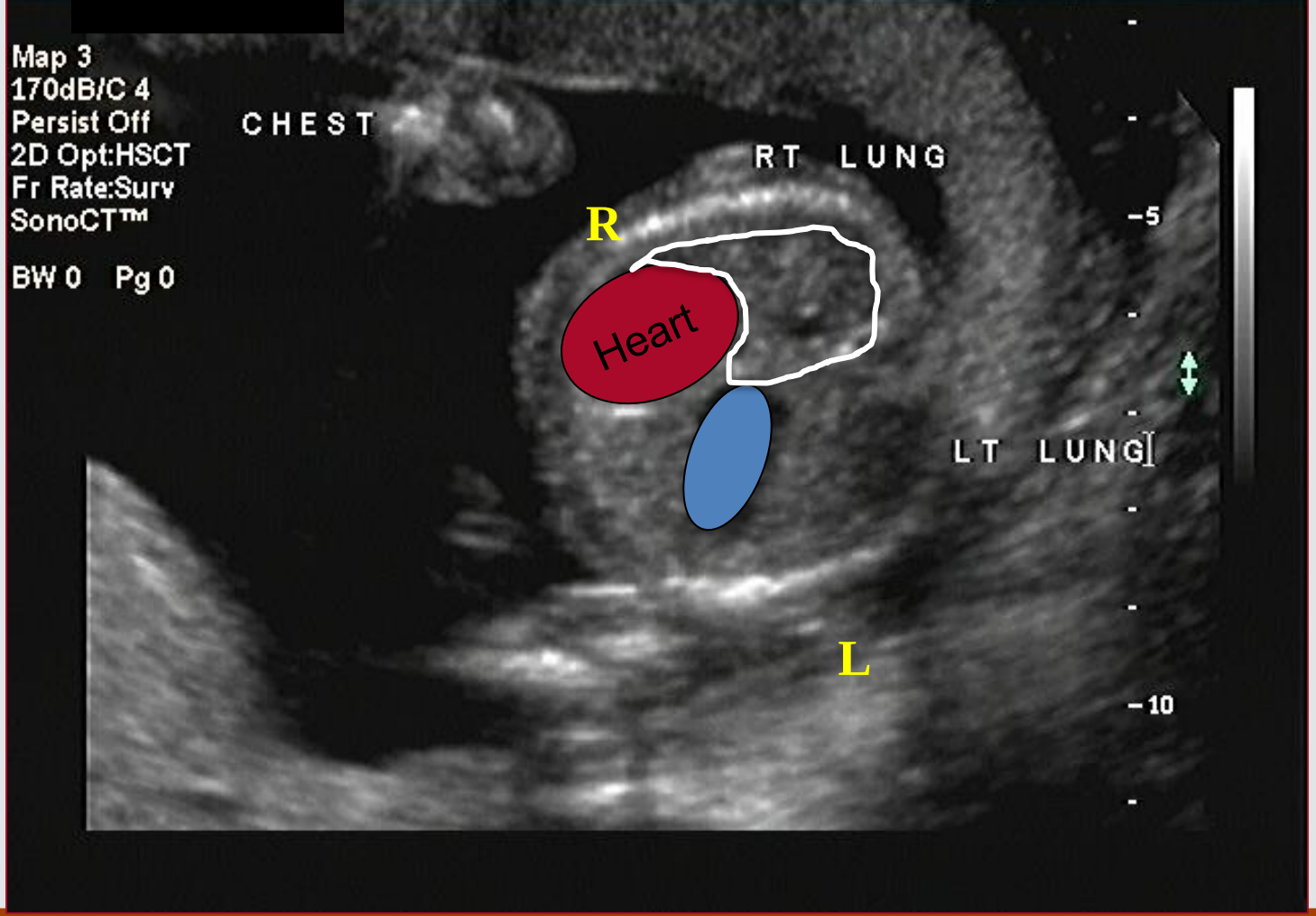
Lung
Heart
LT LUNG
L
-5
-10


Map 3
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2D Opt:HSCT
Fr Rate:Surv
SonoCT™
BW 0 Pg 0
CHEST
RT LUNG
R
Heart
LT LUNG
L
-5
-10

Diaphragmatic Hernia (LHR Ratio)

$$\text{LHR} = \frac{\text{Area of contralateral lung}}{\text{Head circumference}}$$

Diaphragmatic Hernia (LHR Ratio)

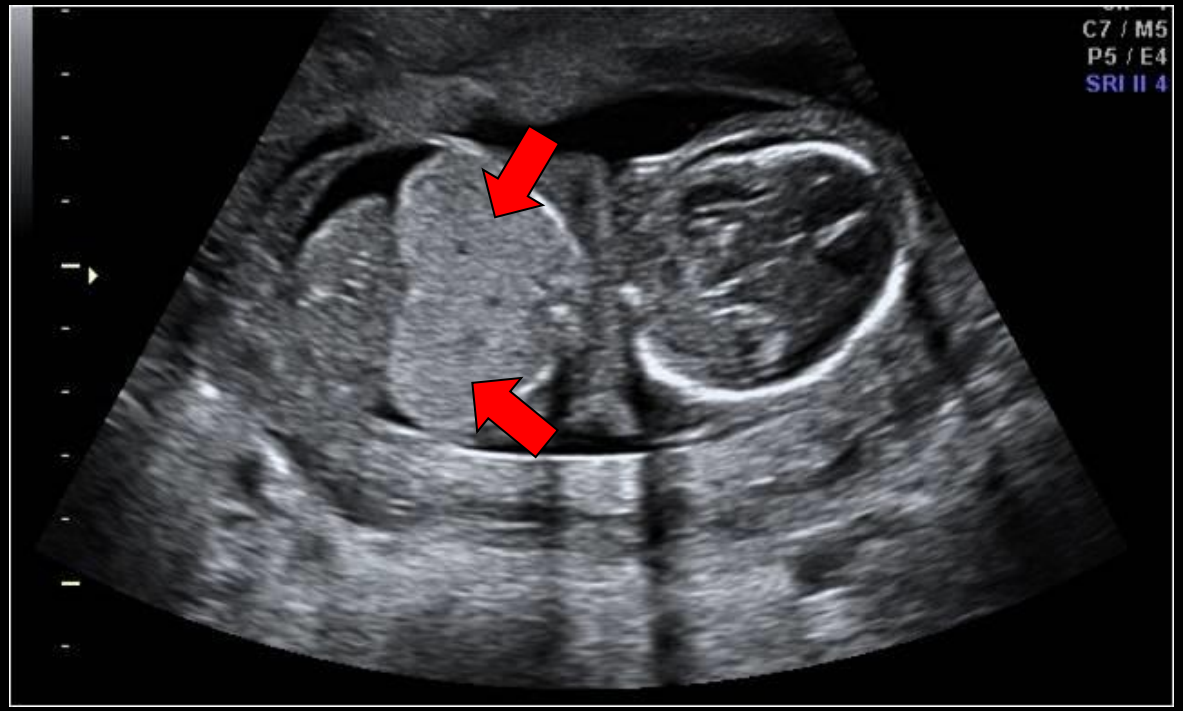
LHR	Liver	N	Survival
> 1.4	NA	10	80%
1.0 – 1.4	↓	7	71%
	↑	7	57%
< 1.0	↓	12	42%
	↑	17	6%

Deprest et al. Semin Perinatol 2005;29:94-103

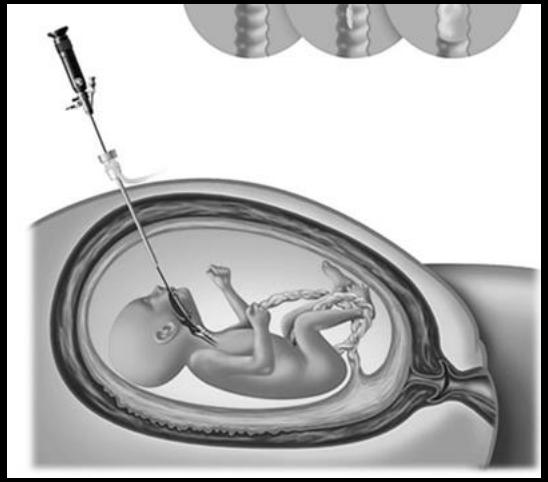
Diaphragmatic Hernia (LHR Ratio)

- Change to “trace” method over AP and transverse measurements
- Change to O/E ratios – value compared to expected for gestational age
  - Mild: O/E > 45%
  - Moderate: O/E: 35 – 45% w/liver up
    O/E: 25 – 35% w/ liver down
  - Severe: O/E < 25%

An Experiment in Nature
(congenital high airway obstruction)



Fetoscopic Placement of Tracheal Balloon for Diaphragm Hernia



ORIGINAL ARTICLE

Randomized Trial of Fetal Surgery for Moderate Left Diaphragmatic Hernia

Jan A. Deprest, M.D., Ph.D., Alexandra Benachi, M.D., Ph.D., Eduard Gratacos, M.D., Ph.D., Kypros H. Nicolaides, M.D., Christoph Berg, M.D., Ph.D., Nicola Persico, M.D., Ph.D., Michael Belfort, M.D., Ph.D., Glenn J. Gardener, M.D., Ph.D., Yves Ville, M.D., Ph.D., Anthony Johnson, M.D., Francesco Morini, M.D., Ph.D., Mirosław Wielgoś, M.D., Ph.D., Ben Van Calster, Ph.D., and Philip L.J. DeKoninck, M.D., Ph.D., for the TOTAL Trial for Moderate Hypoplasia Investigators*

N Eng J Med 2021;385:119-29

Criteria:

- O/E LHR: 25 - 35% OR 35 - 45% w/liver up
  35 - 45% w/liver up
- TO: 30 - 3116/7 wks EGA to 34 - 34 6/7 wks

Outcome:

- Survival to neonatal discharge
  63% vs 50% (RR: 1.27)
- No O_2 at 6 months
  54% vs 44% (RR: 1.23)

Tracheal occlusion NOT indicated for moderate CDH

ESTABLISHED IN 1812 JULY 8, 2021 VOL. 385 NO. 2

Randomized Trial of Fetal Surgery for Severe Left Diaphragmatic Hernia

J.A. Deprest, K.H. Nicolaides, A. Benachi, E. Gratacos, G. Ryan, N. Persico, H. Sago, A. Johnson, M. Wielgoś, C. Berg, B. Van Calster, and F.M. Russo, for the TOTAL Trial for Severe Hypoplasia Investigators*

N Eng J Med 2021;385:107-18

Criteria: O/E LHR: < 25%

TO: 27 – 29 6/7 wks EGA to 34 – 34 6/7 wks EGA

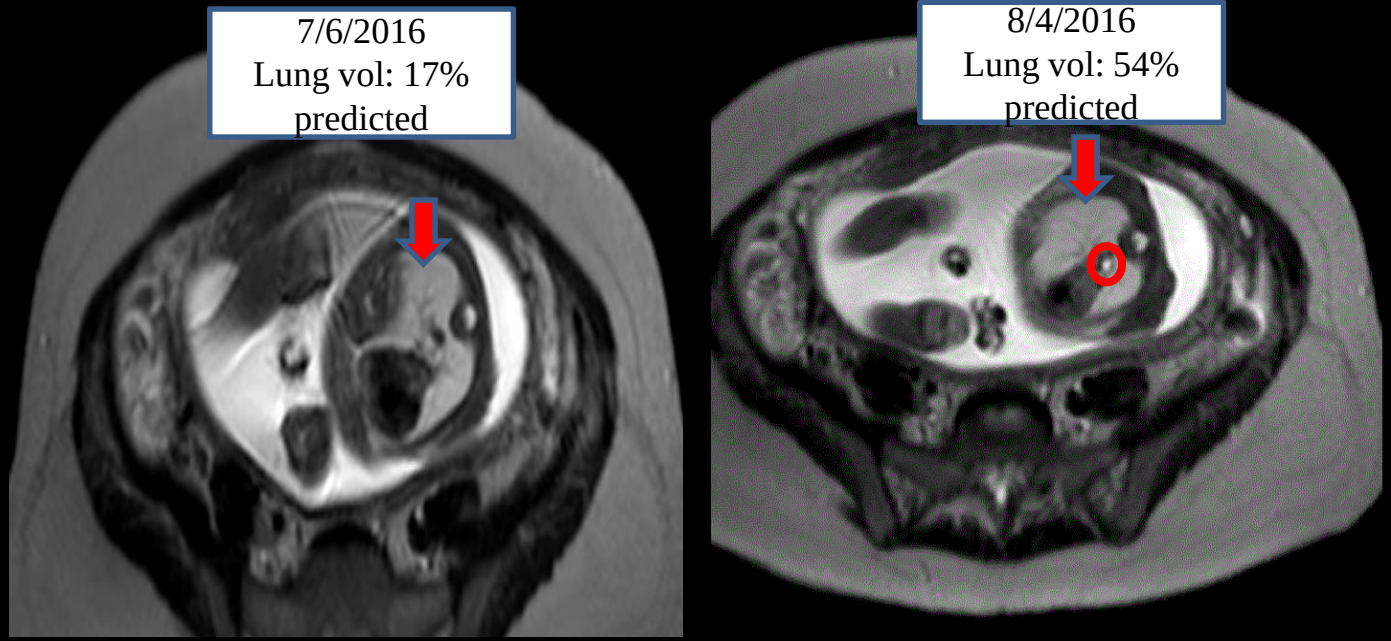
Outcome: Survival to neonatal discharge

- 47% vs 11% (RR: 4.51)

Tracheal occlusion indicated for severe CDH

- ***Normal chromosomes***
- ***No other major fetal anomaly***

Fetoscopic treatment of diaphragm hernia



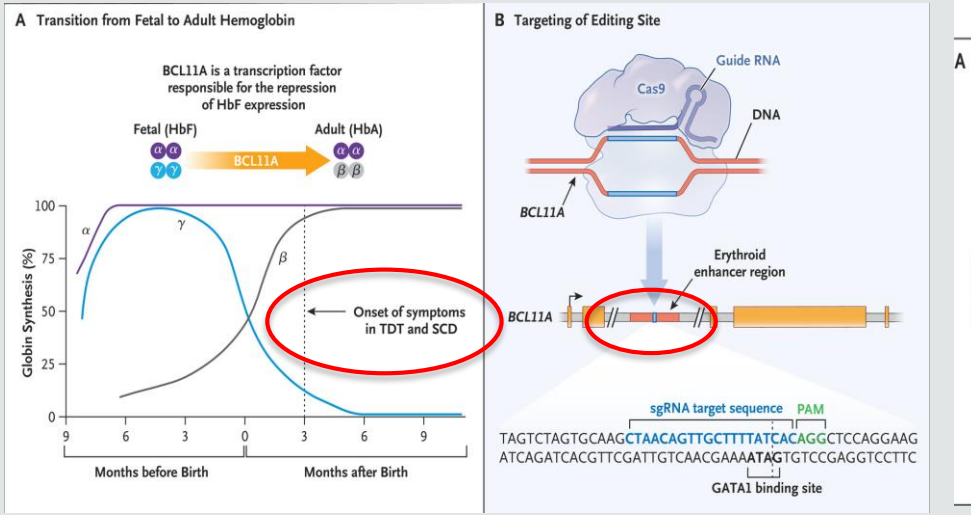
What's On the Horizon for Fetal Therapy?

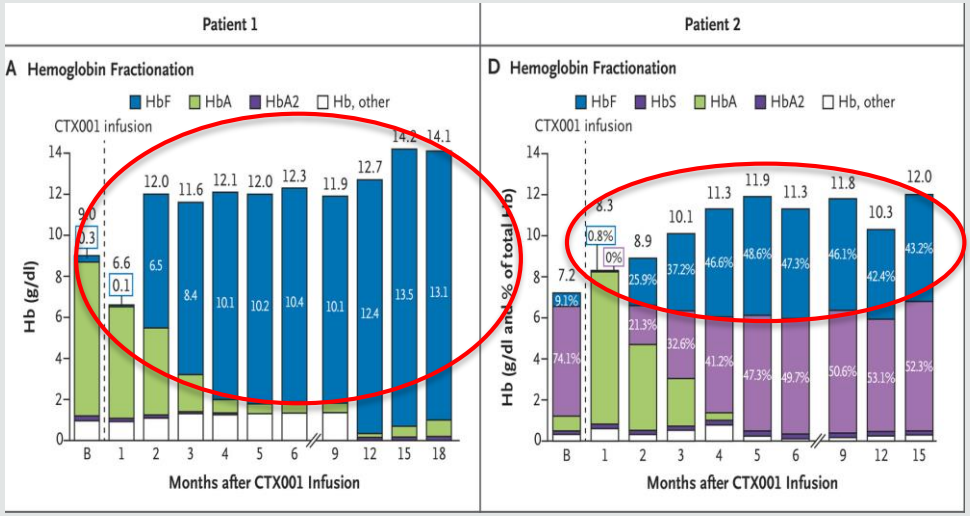
ORIGINAL ARTICLE BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

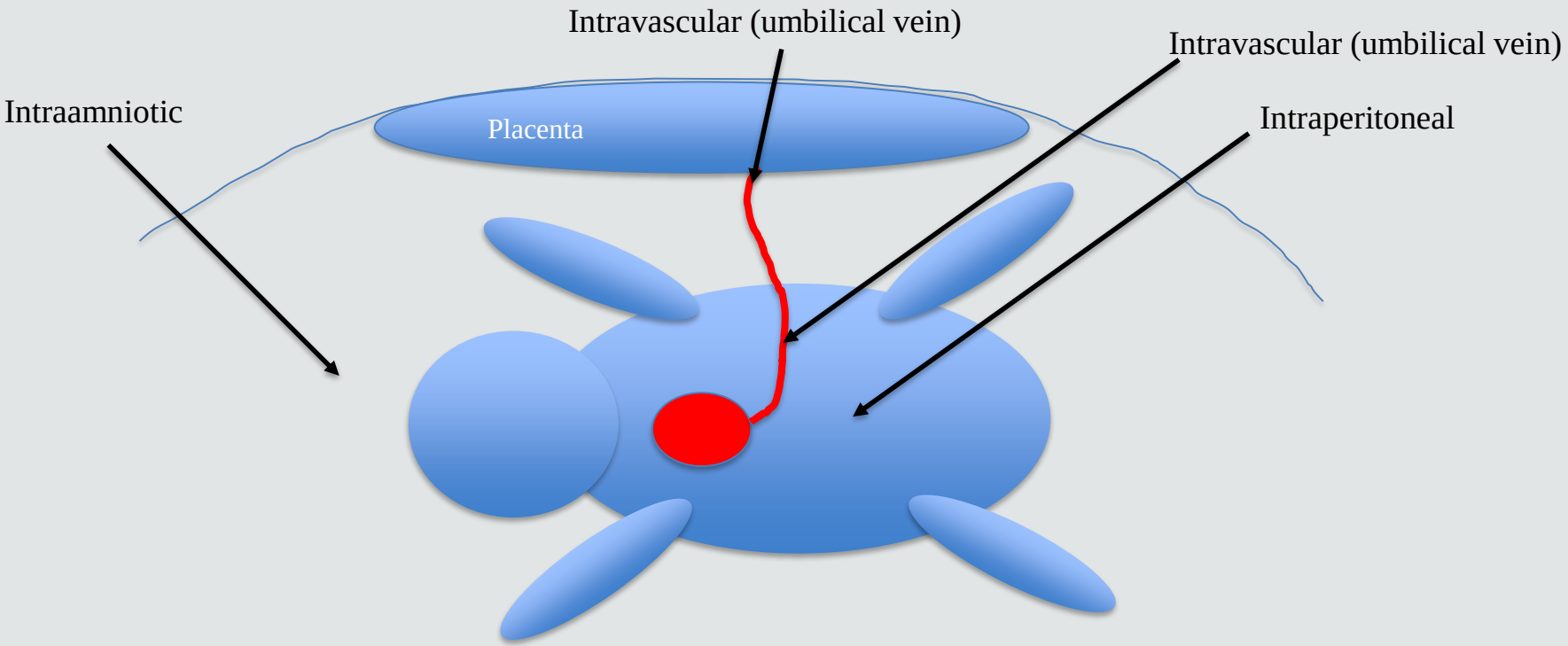
Haydar Frangoul, M.D., David Altshuler, M.D., Ph.D., M. Domenica Cappellini, M.D., Yi-Shan Chen, Ph.D., Jennifer Domm, M.D., Brenda K. Eustace, Ph.D., Juergen Foell, M.D., Josu de la Fuente, M.D., Ph.D., Stephan Grupp, M.D., Ph.D., Rupert Handgretinger, M.D., Tony W. Ho, M.D., Antonis Kattamis, M.D., et al.

January 21, 2021
N Engl J Med 2021; 384:252-260





Routes for Gene Therapy

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