Fetal Intervention
Update 2017

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Disclosures

Receive royalty payments for authorship of the chapters on twin twin transfusion syndrome in UpToDate®

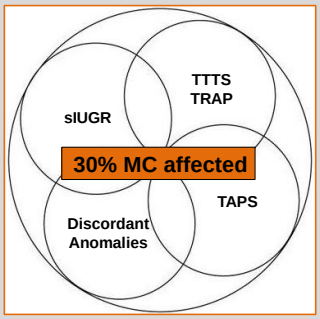
Definition of Maternal-Fetal Surgery

- 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

Objectives

- Review current clinical procedures and potential future maternal fetal interventions
  - Twin twin transfusion (TTTS)
  - Fetal myelomeningocele (fMMC)
  - Fetal diaphragm hernia ~ FETO

Complicated Monochorionic Multifetal Pregnancies



Outcome of MCDA twin gestations in the era of invasive fetal therapy

Survival		
Twin live births	172	85%
Singleton	15	7%
Double demise	15	7%
Complication		
TTTS	18	9%
sIUGR	30	15%
Losses		
Total	11% (TTTS ~ 42%)	
< 24 weeks	84%	
≥ 24 weeks	16%	

Hidden Mortality of MC Twins
Extra loss in MC twins is due to complications placental anastomoses

Lewi et al., 2008

Diagnosis

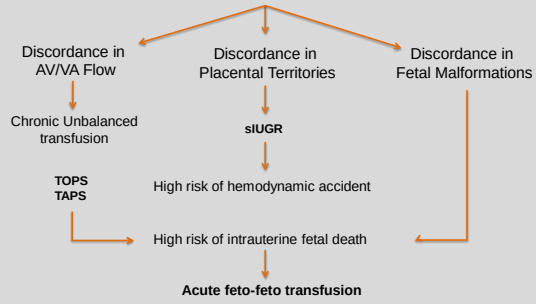
*"There is **NO** diagnosis of twins.*

The only diagnosis is a monochorionic or dichorionic twin gestation.

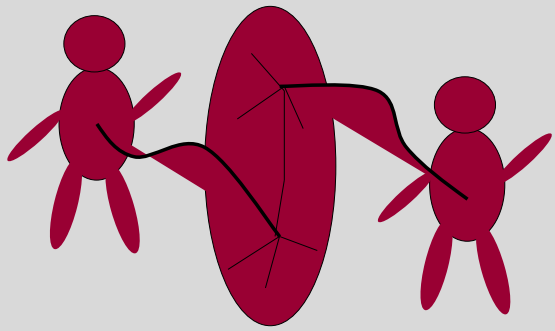
*This should be written in capital **red** letters on the front of the chart at 8 - 10 weeks".*

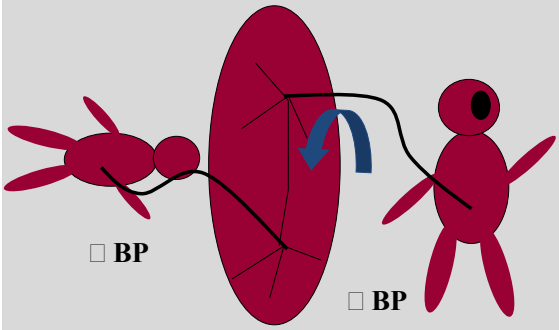
K Nicolaides, 02/27/09

Monochorionic Twin Pregnancy Interfetal Anastomoses



Gratacos E et al Fetal Diagn Ther 2012;32:145-155





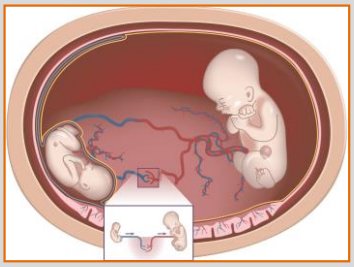
Acute Twin Twin Transfusion Monochorionic Multifetal

- **Perimortem TTTS**
  - Transfusion from surviving twin into dead fetus
  - 18-34% brain injury
  - 15% co-twin demise
  - Optimal treatment not known
- **Acute Perinatal TTTS ~ Intrapartum**
  - 2-5%
  - Acute shifts in blood pressure differences
  - Discordant hemoglobin values > 5g/dL
  - Treatment
    - Donor ~ O2 and volume expansion ~ transfuse w/ RBC
    - Recipient ~ partial exchange transfuion

Chronic Twin-Twin Transfusion Syndrome

Twin Oligohydramnios Polyhydramnios Syndrome
TOPS

Twin Twin Transfusion Syndrome "the common denominator"

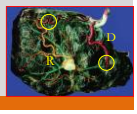


Monochorionic Twins Pathophysiology of TTTS

Net transfer of blood or other vasoactive substance from one fetus (donor) to the other (recipient) via placental vascular communications

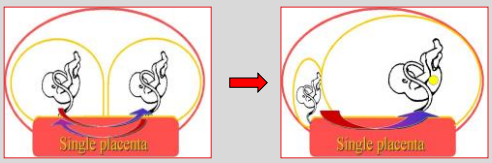
- Arterio-arterial
- Veno-venous
- Arterio-venous
- Deep, unidirectional flow

Pathophysiologic evidence is indirect



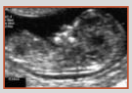
Twin Twin Transfusion Syndrome Diagnosis

- Single placenta
- Discordant amniotic fluid volumes
  - Polyhydramnios (MVP > 8cm) [< 20 wks; > 10 cm ≥ 20 wks]
  - Oligohydramnios (MVP >2cm)
- Concordant for sex



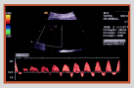
Prediction of Twin Twin Transfusion

Nuchal Translucency



Folding Intertwin Membrane

Arterio-arterial anastomoses



Velamentous Cord Insertion

Timely Diagnosis of TTTS by Biweekly 2nd Trimester Sonography and Patient Education

Monochorionic twins TTTS	**(17%)**
Ultrasound Screening*	
Nuchal translucency	
Membrane folding	
EFW	
Deepest vertical pocket⇧	50%
Doppler: UA, UV, DV	
Patient Education	
Increase Abdominal Girth	50%
Uterine Contractions	

Recommendations:
- Biweekly ultrasounds >16 weeks for all MC Twins
- Detailed patient education

Sueters M et al Ultrasound Obstet Gynecol 2006;28:659

Twin-Twin Transfusion Syndrome Staging

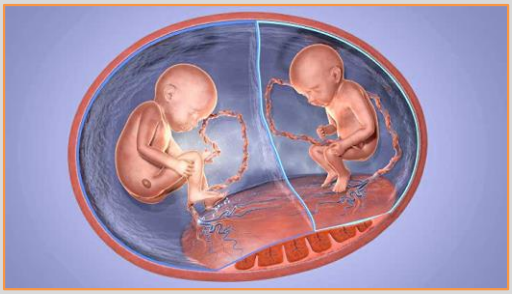
Stage I	Oligohydramnios(<2cm) with Polyhydramnios(>8cm)
Stage II	Discordant fluid volume No bladder in the donor twin
Stage III	Doppler flow- absent or reversed in umbilical artery or ductus venosus, pulsatile flow in the umbilical vein
Stage IV	Hydrops in one or both fetuses
Stage V	One or both fetuses have died

Quintero R et al J. Perinatol 1999;19:55

Treatment for TTTS

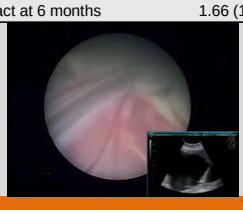
- Serial Amnioreduction
- Amnioreduction w/ Septostomy
- Selective reduction of umbilical cord occlusion
- Fetoscopic laser ablation of placental anastomoses
  - Sequential laser
  - Gestational age limits [16-26 wks]
  - Contraindications
    - Short Cervix ~ center specific
    - PROM
    - Chorioamnion Separation
    - Hemorrhage/Hematoma

TTTS
Laser Photocoagulation



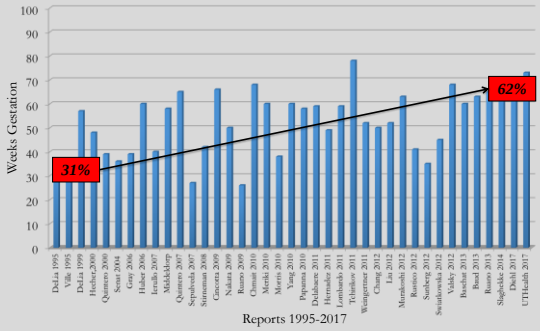
Intervention for the treatment of TTTS
Laser vs. Amnioreduction

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)



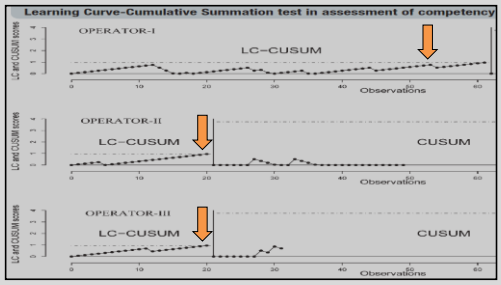
The Cochrane Collaboration 2008

Dual Survival Rates
TTTS Post Laser



Akkermans J et al Fetal Diag Ther 2015;38:241-253

Laser Learning Curve



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

The Fetal Center
30-day Survival Rate ~ Procedure GA
(09/11-08/17)

Gest Age Procedure	TOTAL	Twins	Singleton	None
16-18 weeks	89	65%	20%	15%
19-21 weeks	132	77%	8%	15%
22-24 weeks	75	75%	14%	11%
25-27 weeks	27	70%	30%	
Summary	323	72%	15%	13%

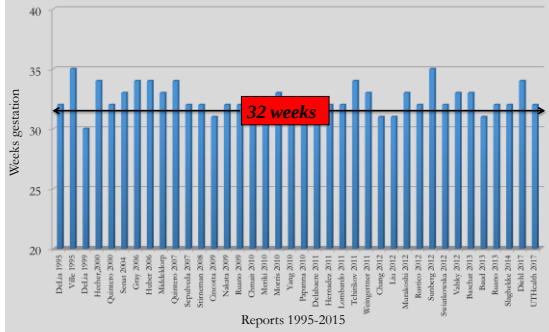
Preoperative predictors of IUFD after laser photocoagulation for TTTS

Study	Variable	IUFD	P
Zikulnig L 1999	Amnioreduction Intertwin discordant AC A/R a-wave DV	Both Donor Recip	0.038 0.004
Martinez J, 2003	AREDF UA R A-wave DV	Donor Donor	0.001 0.007
Skupski D 2010	↓EFW REDF UA R A-wave DV Hydrops	Donor Donor Recip Recip	0.002 0.004 0.007 0.04
Eixarch, E 2013	MCA PSV > 1.5 MOM REDF UA Fetal EFW > 30% GA_Procedure < 22 wks	Recip Donor Donor Donor	0.016 0.033 0.036 0.046

The Fetal Center
30-day Survival Rate ~ TTTS Stage
(09/11-08/17)

TTTS Stage	TOTAL	Twins	Singleton	None
I	43	84%	11%	5%
II	96	76%	9%	15%
III	166	68%	18%	14%
IV	15	67%	26%	7%

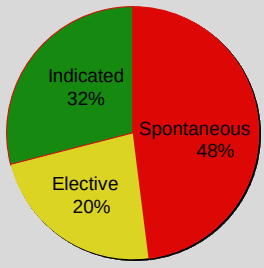
Mean Gestational Age Delivery TTTS Post Laser



Reports 1995-2015

Akkermans J et al Fetal Diag Ther 2015;38:241-253

Etiology for Delivery TTTS Post Laser
(n = 203*)



Prospective study 09/11-12/14

Malshe et al. Am J Obstet Gyneco 2016:214:S41-2.

Risk Factors Associated with Preterm Delivery after Laser ablation in TTTS
(29-33wks)

Variable	Hazard ratio (9% CI)	P
History of prematurity	1.70 (1.11-2.91)	0.015
iPPROM	2.42 (1.93-3.03)	<0.0001
Cervical Length	0.98 (0.98-0.007)	0.004
Amnioinfusion	1.50 (1.20-1.90)	<0.0001
Cannula diameter 12 Fr	1.33 (1.01-1.74)	0.04

Papanna R et al Ultrasound Obstet Gynecol 2014;43:48-53

The Fetal Center
30-day Survival Rate ~ Cervical Length
(09/11-08/17)

Cervical Length	TOTAL	Twins	Singleton	None
≥ 1.5 cm	306	874%	15%	11%
< 1.5 cm	16	44%	12%	44%

TTTS
Neurologic Outcome

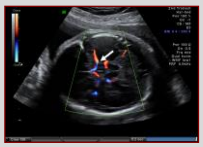
Author	N	Percent follow-up	Age @ follow-up	Major abnormal
Salomon, 2009	73	96%	60 mo	16%
Lopriore, 2017	278	94%	48 mo	CP ~ 5% NDI ~ 6%
Rossi, 2011	895	97%	Birth	6%
	1255	97%	6-48 mo	11%

Cerebral lesions ~ Antenatal origin: 52-67%

Lopriore E: FMF Congress 2017; Sprujit M et al Obstet Gynecol 2012;120:15-20

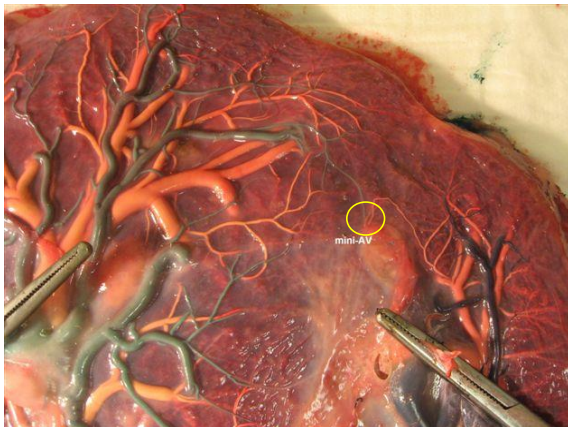
Twin Anemia-Polycythemia Sequence (TAPS)

- Larger intertwin hemoglobin difference w/o signs of TOPS
- Intertwin blood transfusion w/o hormonal imbalance
- Post laser: ex-recipient anemic w/ ex-donor polycythemic
- Spontaneous reported as early as 16 weeks

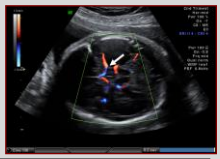


Study	N	Post-laser
Robyr, 2006	101	13%
Habli, 2009	152	2%
Slagehekke,2010	276	8%
		Spontaneous
Lewi et al, 2009	202	5%
Lopriore, 2010	113	5%

Slagehekke F et al Fetal Diagn Therapy 2010



TAPS: Classification

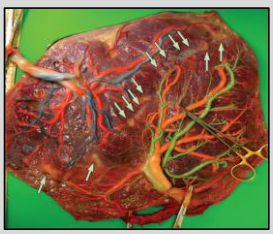


Antenatal	Finding as Doppler Examination
Stage 1	MAC-PSV: Donor > 1.5 & Recipient < 1.0 MOM
Stage 2	MCA-PSV: Donor > 1.7 & Recipient < 0.8 MOM
Stage 3	Stage 1 or 2, with Cardiac compromise in donor
Stage 4	Donor hydrops
Stage 5	IUFD of one or both

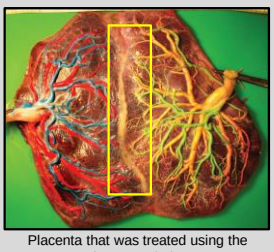
MCA PSV should be included in screening all MC Multifetal pregnancies

Slagehekke F et al Fetal Diagn Therapy 2010

Fetoscopic laser coagulation of the vascular equator versus selective coagulation for TTTS
An open-label RCT



Placenta that was treated using the standard technique



Placenta that was treated using the Solomon technique

Slaghekke F, et al. The Lancent, 2014.(13)62419-8

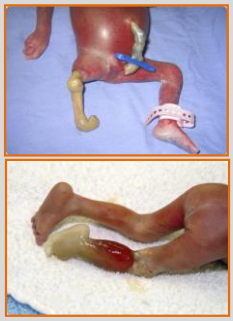
Solomon Trial RCT

Laser Vascular Equator vs. Selective Coagulation

Outome	Solomon Group (234 fetuses)	Standard Laser (270 fetuses)	CI
Primary	34%	49%	0.54 (0.35-0.82)
Overall Survival	74%	73%	NS
ALOS	85%	87%	NS
Dual Survival	64%	605	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

Slaghekke F et al Lancet 2014

Vascular Occlusion Injuries in TTTS



- 95% recipient
- 85% lower limb
- 71% right sided
- Intestinal atresia
- Mechanism
  - Polycythemia
  - Hyperviscosity
  - Hypertension
  - Vascoconstriction

Schrey S et al AJOG 2012

Algorithm for Differential Diagnosis in MC Twins

AF MVP >8 cm (>10 cm) / < 2 cm → Yes → TTTS
Bladder very large / very small-non visible

NO

EFW < 10th % tile (+/- >20-25%) → Yes → sIUGR

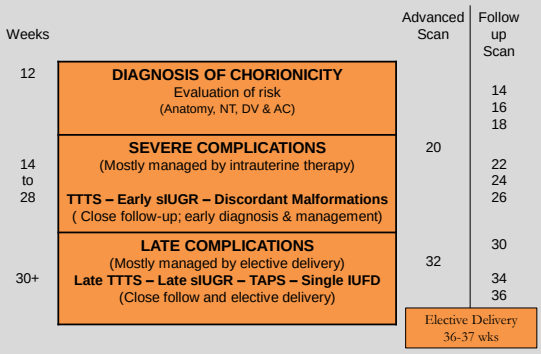
NO

MCA PSV > 1.5 & 0.8 MOM → Yes → TAPS

NO

- AF Discordance
- EFW Discordance

Gratacos E et al Fetal Diagn Ther 2012;32;145-155



Gratacos E et al Fetal Diagn Ther 2012;32:145-155

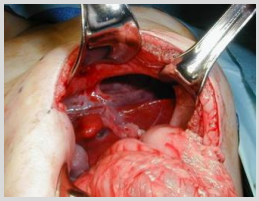
Conclusion Treatment & Management of TTTS

- Expectant Management ~ PMMR 80-90%
- Placental laser photocoagulation
  - Only proven therapy to reverse cardiovascular programming
  - SOC: Stage II-IV at 16-26 weeks
    - Role <16 and >26 weeks preliminary reports promise
    - Stage 1 ?
  - Not a panacea
    - Survival: Dual intact ~ 60-70% with ALOS ~80-90%
    - Donors 60% vs. Recipient 70% [discordance EFW]
    - Developmental impairment 11-16% (cerebral palsy 5%)

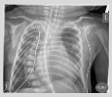
Diaphragmatic Hernia

Diaphragm Hernia

- 1- 4/10,000 live births
- Neonate
  - Defect requiring surgical repair
  - Pulmonary hypoplasia
    - Respiratory insufficiency
    - Pulmonary hypertension
- 2nd tri diagnosis SR > 60%
  - Tertiary referral
    - Advanced imaging
    - Genetic testing
    - Multidisciplinary management



CDH ~ Long Term Morbidity

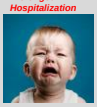

Scoliosis


Prolonged Hospitalization


Feeding Intolerance


Pulmonary HTN


Multiple Operations

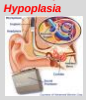

GERD


Pulmonary Hypoplasia


Infection

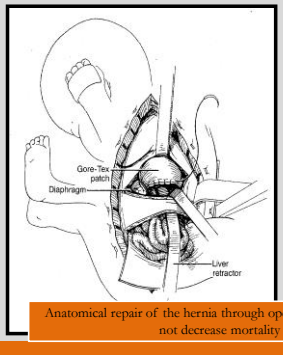

Chest Wall Deformity

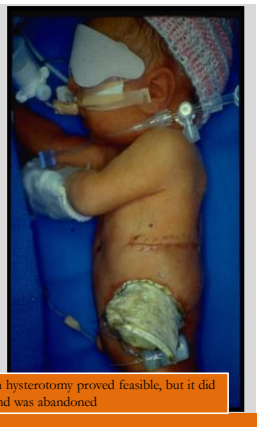

Neurodevelopmental Outcomes


Hearing Problems


Chronic Lung Disease

CDH: Open Fetal Repair





Anatomical repair of the hernia through open hysterotomy proved feasible, but it did not decrease mortality and was abandoned

Fetal Lamb Tracheal Ligation & CDH Reversal of Structural & Physiologic Effects

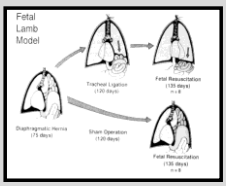
Purpose: Can lung growth be accelerated in the setting of experimental pulmonary hypoplasia.

Method: 95 day gestation fetal sheep were divided into four groups: nephrectomy (NP), NP/TL, TL alone, and sham-operated control animals.

Results: NP smaller lungs than control, NP/TL larger lungs when compared with NP and the controls

Concluded:
(1)TL accelerated lung growth beyond normal limits even in the absence of fetal kidneys;
(2)Lung growth is achieved in part by cell proliferation;
(3)Lung architecture remains relatively normal;
(4)Pulmonary hypoplasia associated with CDH may be preventable by tracheal occlusion

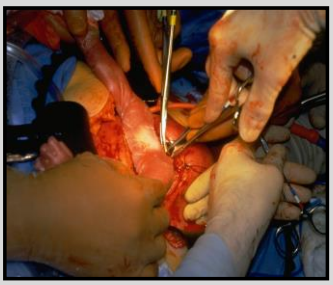
Wilson JM J Pediatr Surg 1993;28:1433



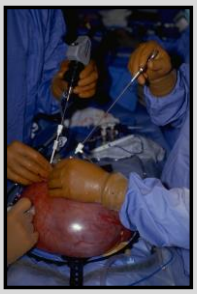
Proposed Tracheal Occlusion For treatment of CDH Section of Surgery Annual meeting 1992 AAP

Fetal Tracheal Clip Application Laparotomy

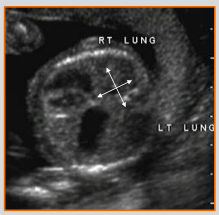
"Open" ~ Hysterotomy



"Fetoscopic" ~2-Port



Sonographic Predictors of Survival in Fetal Diaphragmatic Hernia

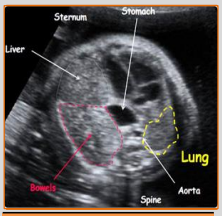


N	Survival	LHR
5	0%	< 0.6
28	57%	> 0.6 - ≤ 1.35
5	100%	> 1.35

- Postnatal survival directly related to LHR
- Large difference in reported results
  - Measured at different gestational ages
  - Method of measuring LHR

Jani J et al. Ultrasound Obstet Gynecol.2007;30:72e6 *Metkus AP J Pediatr Surg 1996;31:14*

Sonographic Predictors of Survival in Fetal Diaphragmatic Hernia



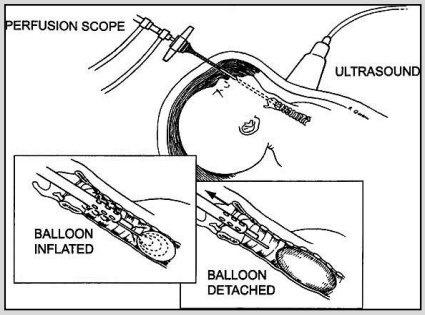
Ultrasound	MRI
LHR O/E	TFLV O/E
Liver ⇑	LiTV
Stomach	Stomach
Vascular Index	

N	Survival	LHR
5	0%	< 0.6
28	57%	> 0.6 - ≤ 1.35
5	100%	> 1.35

- Postnatal survival directly related to LHR
- Large difference in reported results
  - Measured at different gestational ages
  - Method of measuring LHR

Jani J et al. Ultrasound Obstet Gynecol.2007;30:72e6 *Metkus AP J Pediatr Surg 1996;31:14*

FETENDO- PLUG
Fetal endoscopic tracheal occlusion



Diaphragmatic Hernia NIH Randomized Trial

	Standard Treatment	Tracheal Occlusion	P
N	11	13	
PROM	23%	100%	< 0.001
PTL	31%	73%	0.10
Abruption	8%	27%	0.30
GA_ Del	37.0 + 1.5	30.8 + 2.0	< 0.001
Survival 90days	77%	73%	1.0

LHR < 1.4 with liver herniation

Harrison et al. N Eng J Med 2003; 349:1916-24

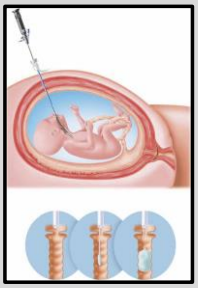
Antenatal Left Sided Diaphragm Hernia
Survival Rates LHR O/E and Liver Position

UCSF

		Eurofetus	
o/e LHR	Liver	N	Survival
<25%	Up	39	15%
	Down	10	30%
25-34%	Up	65	55%
	Down	44	66%
35-44%	Up	27	66%
	Down	47	77%
>45%	Up	16	100%
	Down	67	87%
TOTAL	Up	161	55%
	Down	168	75%

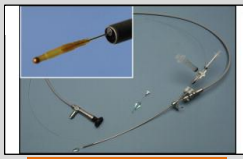
Modified from Deprest et al. 2011

European Consortium Fetoscopic Tracheal Occlusion (FETO)

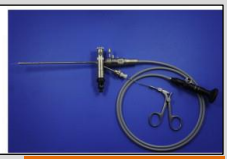


Deprest, et al. Ultrasound Obstet Gyn 24:121, 2004

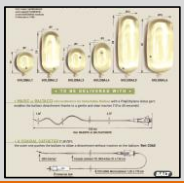
EUROFETUS Modification FETO Instruments



Fetoscope with curved sheath

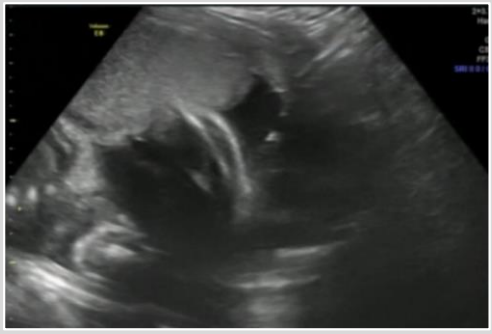


Bronchoscope with forceps



BALT Goldballoon & Catheter
Designed especially for the embolisation of arterio-venous malformations and blood vessel occlusion.

Deprest, J. Seminars Fetal & Neonatal Med, 2014; 19: 338 - 348



Isolated Left Side DH ~ 29 4/7 weeks

Severe Left Sided CDH treated with FETO Predictor of Postnatal Survival O/E LHR

Variable	N	Survival
Total	144	54%
o/e LHR (%)		
< 15	15	20%
16-20	53	59%
21-25	56	54%
26-30	20	70%

Doubling Survival Rate

FETO in Severe CDH
Associated with a substantial improvement in survival.

Jani J et al Ultrasound Obstet Gynecol 2009

Cochrane Database of Systematic Review Conclusion

•The current evidence is too limited by small numbers of pregnancies and variable methodological quality of the trials to date to recommend intervention (FETO) in pregnancy for women and their unborn babies with CDH.

RCT Study	N
Harrison, MR, NEJM 2003	24
Ruano R, UOG, 2012	41

Cochrane Database Syst Rev. 2015 Nov 27;(11)

www.TOTAL trial.eu

Tracheal

Occlusion

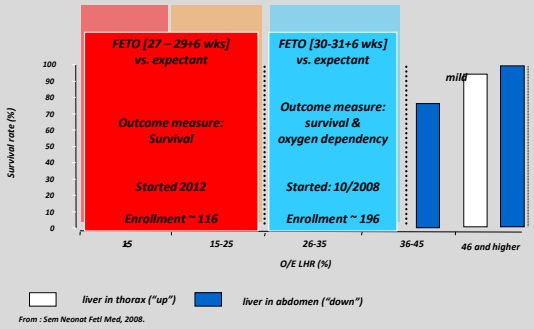
To

Accelerate

Lunggrowth

www.totaltrial.eu

TOTAL Trial ~ Two randomized trials



TOTAL Trial Hypothesis

Prenatal intervention, fetoscopic tracheal occlusion will have a 50% increase of the expected survival rate in fetuses with isolated CDH and severe pulmonary hypoplasia

TOTAL Trial

Inclusion

- Singleton fetus
- Isolated left-sided CDH
- Normal Karyotype
- Severe Group
  - O/E LHR <25 %
  - Irrespective of liver position
- Moderate Group
  - O/E LHR 25-34.9% , liver up or down
  - O/E LHR 35-44% liver up

Exclusion

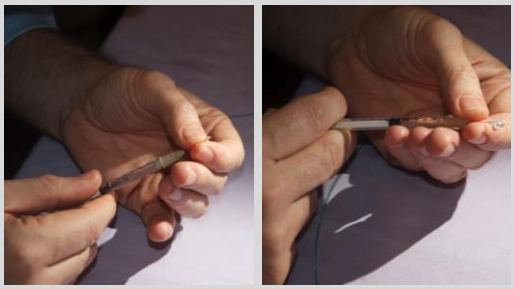
- Maternal contraindication to fetal intervention
- Technical or maternal limitation to fetoscopy
- Hx preterm labour
- Cervix length <15 mm
- Refusal to remain in proximity to FETO center during time period of airway occlusion

Postnatal Treatment
Expectant management during pregnancy postnatal repair.
Standardized neonatal intensive care

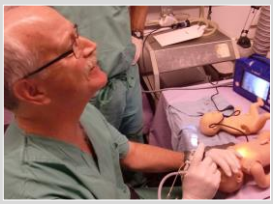
Total Trial
FETO Participating Center Requirments

- **FETO Center**
  - Fetoscopic Program ~ 36/year
  - Postnatal CDH Program ~ 7/year
- **Local PI**
  - Profiency
    - Participating in 15 cases
    - 5 cases performed locally ~ Feasibility Studies

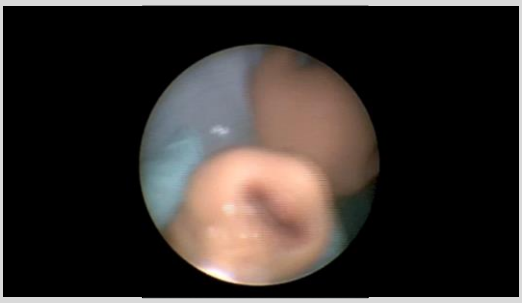
BALT Occlusive Device



TOTAL Team Training
Simulation and Animal



FETO Simulation Model



Pilot Trial of FETO in Left CDH
Feasibility Study

Study Type: Interventional

Study Design:

- Endpoint: Safety/Efficacy Study
- Interventional Model: Single group assignment
- Masking: Open Label
- Primary Purpose: Treatment

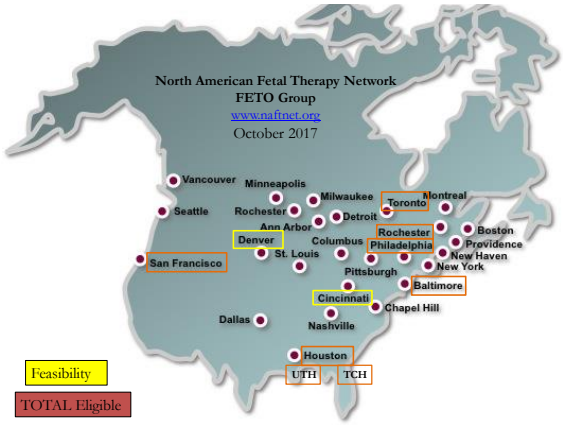
Primary Outcomes

- Successful placement & removal of BALT Goldbal2 balloon
- Gestational age of delivery

Secondary Outcomes

- Lung Volume & LHR after FETO
- Survival 6 month

Ultimate goal to enter TOTAL Trial



TOTAL TRIAL ~LIMITATIONS

- Backdoors ~ Balloons placed outside the trial
- European ~ Lack of Equipoise
  - ***Pessimistic***: survival rate with expectant management
  - ***Optimistic***: suggest outcomes better with FETO

**Jani J et al UOG 2009*

TOTAL Trial & CDH

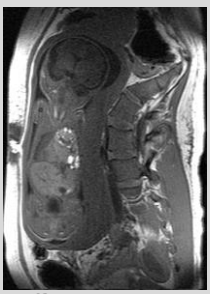
- CDH is a rare disorder
- Concentrating treatment in high volume regional centers with expertise ~ common sense
- Experience is related to efficacy
  - Improved perioperative assessment
  - Shorten "learning curve"
    - Shorten Operative times
    - Reduced PPROM
  - Overall Maternal Fetal Outcomes

Cochrane Database of Systematic Review Conclusion

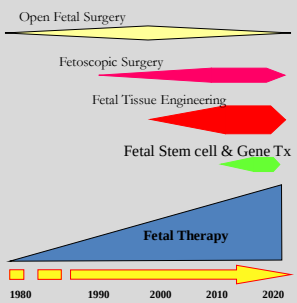
- Further high-quality trials are need in this area
- FETO should only be offered within the framework of ongoing clinical trial.

Cochrane Database Syst Rev. 2015 Nov 27;(11)

Time Line for Future Events in Fetal Intervention



CDH with Liver Herniation



Fetal surgery for spina bifida: A paradigm shift for modern fetal centers

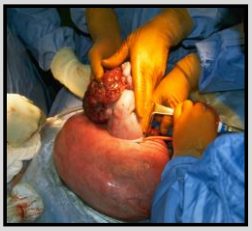
KuoJen Tsao, MD
Professor of Pediatric Surgery
Professor of Obstetrics and Gynecology
University of Texas McGovern Medical School at Houston
Co-Director, The Fetal Center
UTHealth | McGovern Medical School

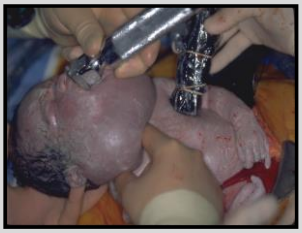
Children's Memorial Hermann Hospital

Fetal Surgery

Application of established surgical techniques to the unborn baby

- During gestation
- At end of gestation

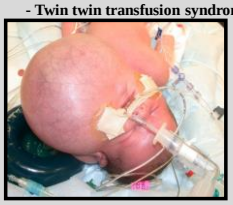




Fetal Surgery

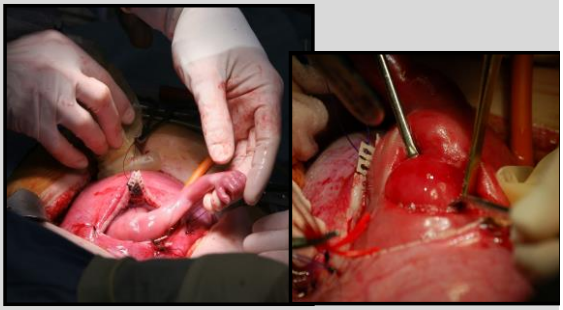
To improve perinatal outcome for fetuses with malformations.

- To prevent fetal death
  - **Lung masses**
  - **Sacrococcygeal teratoma**
  - **Twin twin transfusion syndrome**



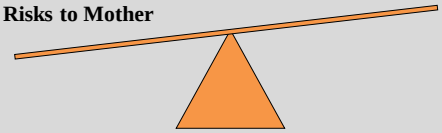
- To prevent neonatal death or reduce long-term morbidity
  - **Giant neck masses**
  - **Congenital diaphragmatic hernia**
  - **Congenital heart lesions**
  - **Spina bifida***

Fetal Surgery

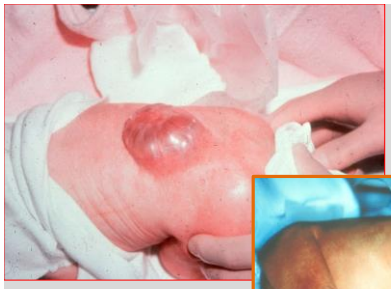


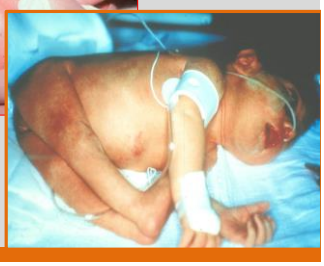
Fetal Surgery: Balancing Risks

- **Natural hx of fetal anomaly**
- **Fetal surgical risks**
- **Risks to Mother**

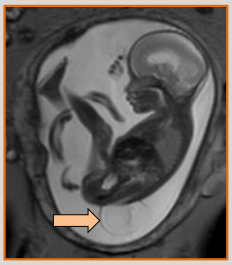


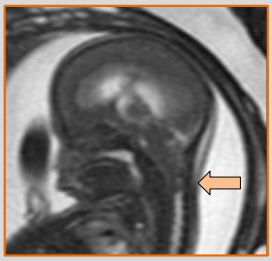
Spina Bifida



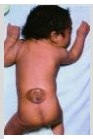


Meningomyelocele with Arnold Chiari Malformation





Spina bifida



4,000 babies are born per year in the United States

Hospital cost after birth:

- Median $29,000 (range:$100-$1,300,000)

Cost of caring for a spina bifida:

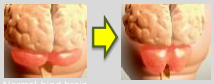
- $636,000 per person for life
- $200 million per year

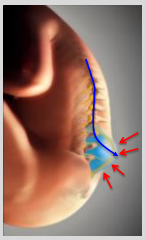
Long-term morbidity associated with spina bifida

- Unable to independently walk
- Bowel and bladder control problems
- Hydrocephalus- shunt placement
- Mental retardation
- Sexual dysfunction

www.cdc.gov

Rationale for In-utero Spina Bifida Repair





#1. Prevent leakage of CSF

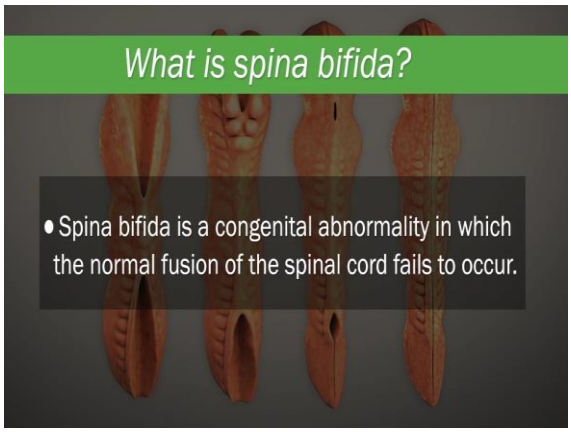
⇩

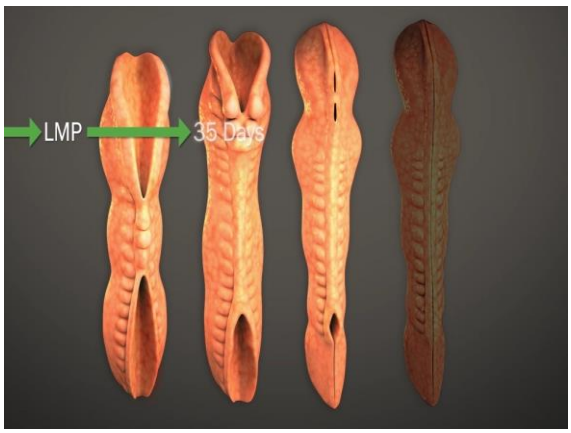
Reverse Chiari II malformation

#2. Prevent damage to spinal cord

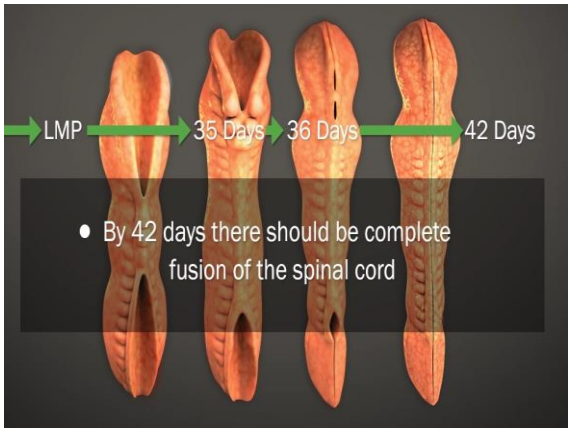
⇩

Preserve spinal cord function

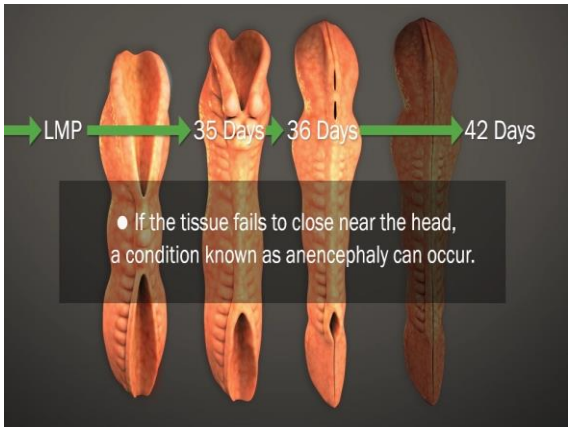


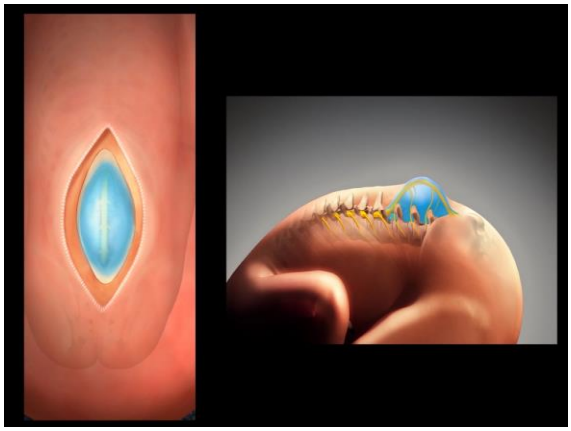



LMP
35 Days
36 Days
• At 36 days there is almost complete fusion of the spinal cord .

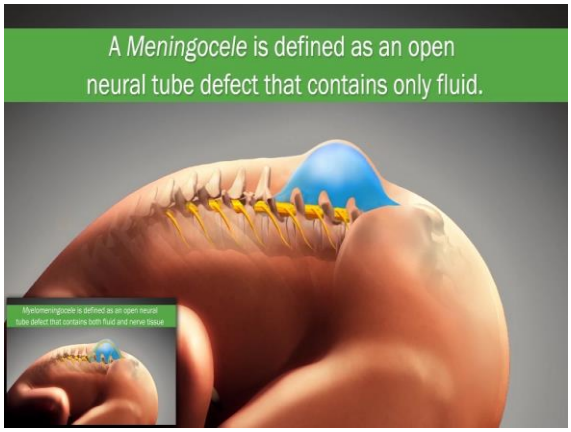

LMP
35 Days
36 Days
42 Days
• By 42 days there should be complete fusion of the spinal cord

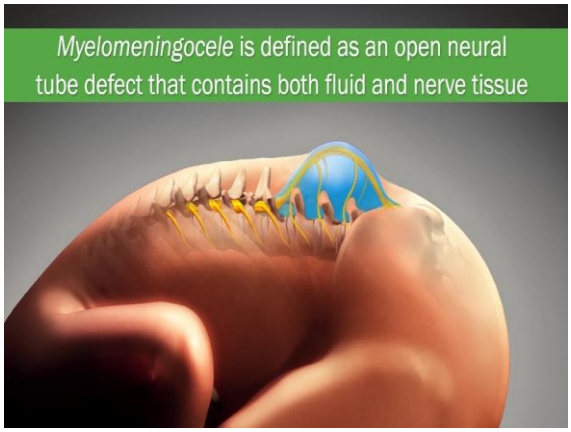

LMP


LMP
35 Days
36 Days
42 Days
• If the tissue fails to close near the head, a condition known as anencephaly can occur.

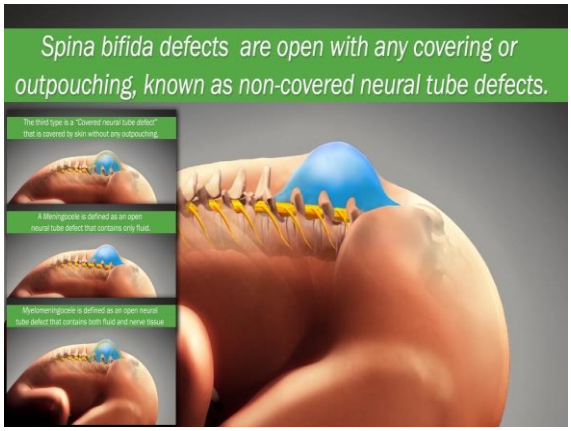


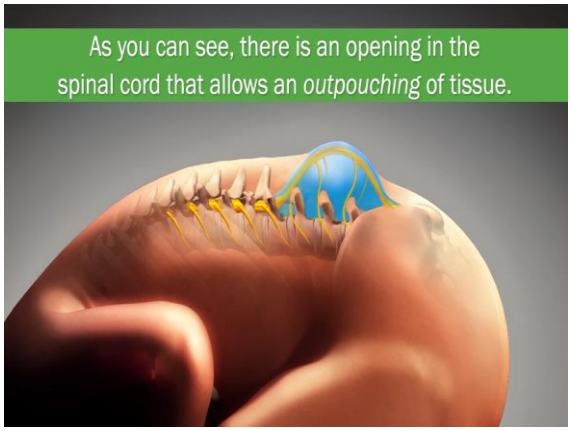

There are four types of spina bifida

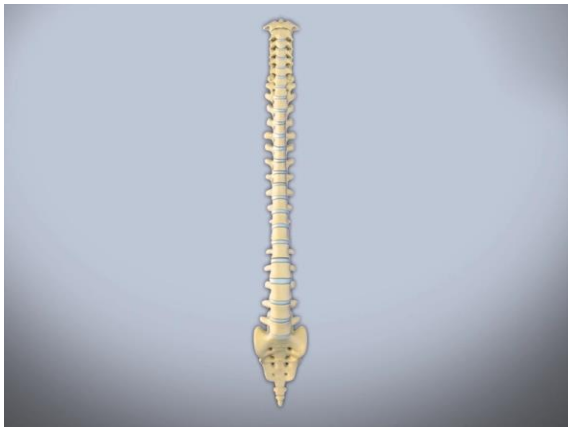

A *Meningocele* is defined as an open neural tube defect that contains only fluid.
Myelomeningocele is defined as an open neural tube defect that contains both fluid and nerve tissue

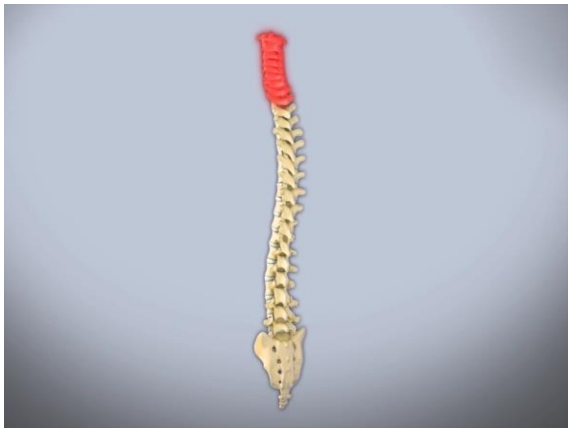

Myelomeningocele is defined as an open neural tube defect that contains both fluid and nerve tissue

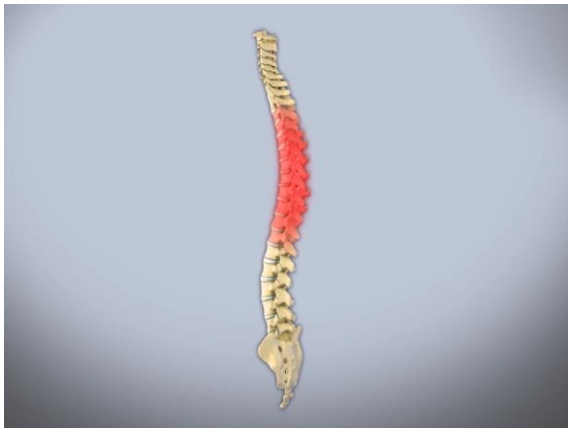

The third type is a *"Covered neural tube defect"* that is covered by skin without any outpouching.
A Meningocele is defined as an open neural tube defect that contains only fluid.
Myelomeningocele is defined as an open neural tube defect that contains both fluid and nerve tissue

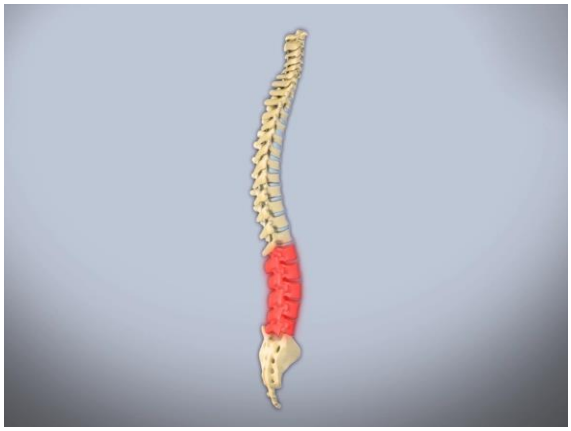

Spina bifida defects are open with any covering or outpouching, known as non-covered neural tube defects.
The third type is a "Covered neural tube defect" that is covered by skin without any outpouching.
A Meningocele is defined as an open neural tube defect that contains only fluid.
Myelomeningocele is defined as an open neural tube defect that contains both fluid and nerve tissue

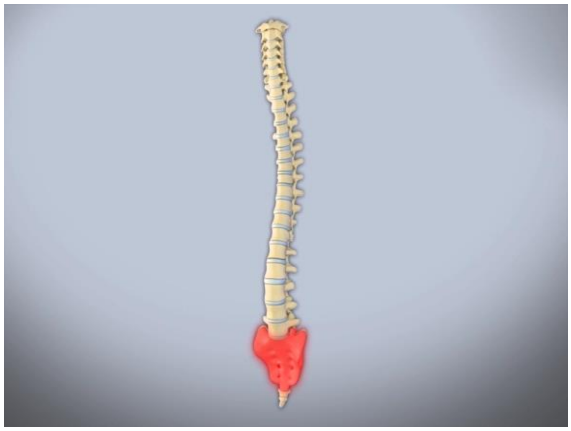

As you can see, there is an opening in the spinal cord that allows an *outpouching* of tissue.

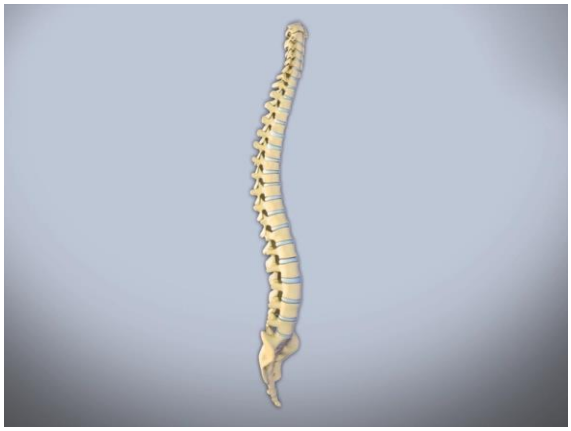


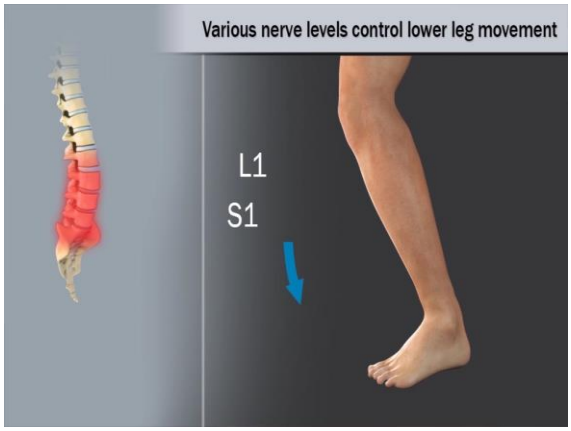


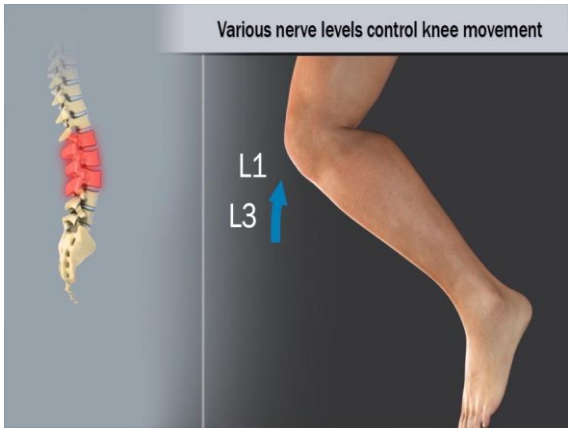


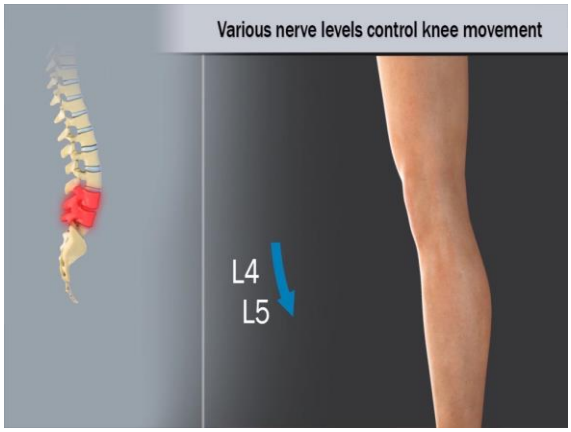


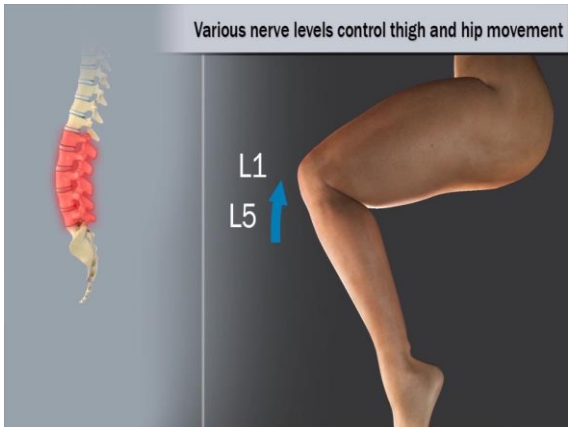


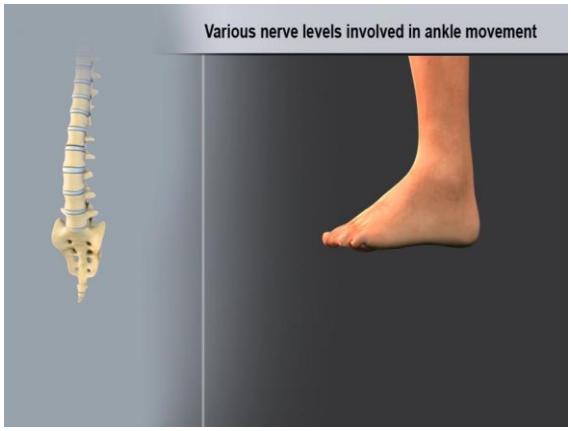


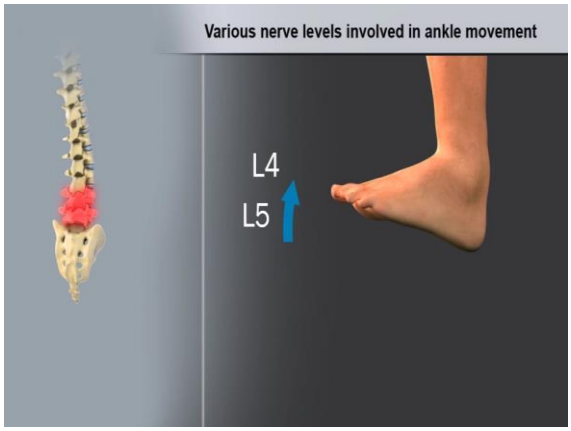

Various nerve levels control lower leg movement
L1
S1

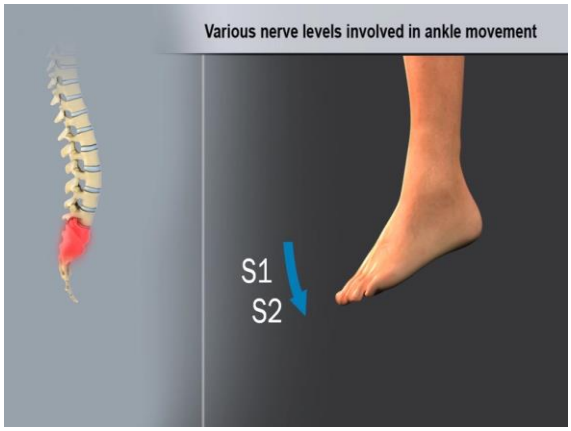

Various nerve levels control knee movement
L1
L3

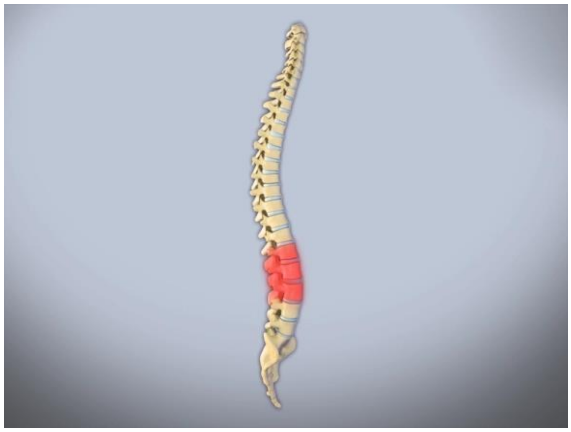

Various nerve levels control knee movement
L4
L5

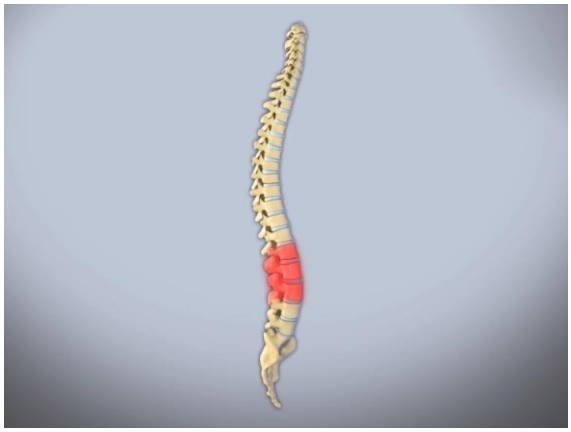

Various nerve levels control thigh and hip movement
L1
L5


Various nerve levels involved in ankle movement


Various nerve levels involved in ankle movement
L4
L5


Various nerve levels involved in ankle movement
S1
S2





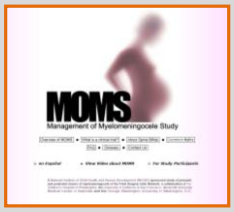
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 17, 2011 VOL. 364 NO. 11

A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele

Management of Myelomeningocele Study (MOMS Trial)

- Fetal Surgery vs Routine Care
- NIH funded
- 3 Centers
  - University of California, San Francisco
  - Children's Hospital of Pennsylvania
  - Vanderbilt Medical Center
- 8 years
- $22.5 million



Goal

To compare the safety and efficacy of *in utero* repair of myelomeningocele with that of the standard postnatal repair

Study Design

- Unmasked randomized trial
- Fetal versus postnatal closure of myelomeningocele
- Sample size 200
- Central preliminary screening and assignment to MOMS center
- Central randomization
- Outcome evaluation by blinded independent investigators

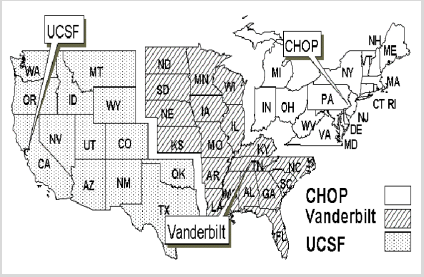
Inclusion Criteria

- Myelomeningocele defect starting between T1-S1
- Evidence of hindbrain herniation
- Singleton pregnancy 19^0 to 25^6 weeks
- Normal karyotype
- Resident of USA
- 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 (< 2.5 cm)
  - cerclage
  - uterine anomaly
  - placenta previa
  - prior spontaneous preterm delivery
- Unable to comply with travel, need for support
- Psychosocial issues preventing compliance
- Fetal kyphosis ≥ 30 degrees
- Maternal IDDM
- Isoimmunization
- Body mass index ≥ 35
- Other contraindications to elective surgery

MOMS Center patient referral distribution



Evaluation at MOMS Center

- 2-day comprehensive evaluation
- Medical Evaluation
  - History and physical
  - Ultrasound
  - Fetal MRI
  - Fetal echocardiogram
  - Beck Depression Inventory
- Consultation with team
  - Fetal surgeon
  - Perinatologist
  - Neurosurgeon
  - Neonatologist
  - Anesthesiologist
  - Social worker
  - Ethicist
  - Nurse coordinator

If Randomized to Prenatal Surgery

- Surgery 1-3 days after randomization
- Before 26 weeks
- Standardized surgical technique
- Postoperative tocolytic therapy
- Patient in local accommodation until delivery
- Two weeks bedrest post-op
- Weekly visits to MOMS center
- Delivery by C-section at 37 weeks

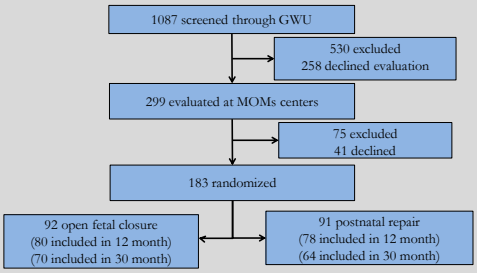
If Randomized to Postnatal Surgery

- Patient returned home for prenatal care
- Monthly ultrasounds by local physician
- Return to MOMS center at 37 weeks for fetal lung maturity testing
- Cesarean delivery if fetal lung maturity
- Neonatal repair by MOMS neurosurgical team

MOMs Follow-up Exams

- Patient, support person and infant travel to MOMS center
- 12 and 30 months
- Independent follow-up teams
  - Pediatrician
  - Psychologist
- Appointed by the Data Coordinating Center
  - No affiliation with MOMS Center
- Blinded to treatment assignment

MOMS Trial Accounting



Primary Outcome at 12 months

- Death
- Need for ventricular decompressive shunting
  - Need determined by independent neurosurgeons with defined by objective criteria
  - Blinded to randomization

Infant Outcomes at 12 Months

	Prenatal Surgery (n=78)	Postnatal Surgery (n=80)	RR (95% CI)	P value
Primary Outcome (%)	68	98	0.70(0.58-0.84)	<0.001
Death	3	0		
Shunt criteria met	65	92		
Placement of shunt (%)	40	82	0.48(0.36-0.640	<0.001
Any hindbrain herniation (%)	64	96	0.67(0.56-0.81)	<0.001
None	36	4		
Mild	40	29		
Moderate	19	45		
Severe	6	22		

Secondary Outcome at 30 months

- BSID - mental development index (MDI)
- Difference between the motor and lesion level
  - Lesion level determined radiographically
  - Functional level examination
    - Motosensory
    - Somatosensory

Infant Outcomes at 30 months

	Prenatal Sx N=64	Postnatal Sx N=70	P value
Primary outcome score	148.6±57.6	122.6±57.2	0.007
BMDI - MDI	89.7±14.0	87.3±18.4	0.53
Difference between anatomic level & functional level	0.58±1.94	-0.69±1.99	0.001
Difference (%)			
≥ 2 levels better	32	12	0.005
1 level better	11	9	
no difference	23	25	
1 level worse	21	25	
≥ 2 levels worse	13	28	0.03

Infant Outcomes at 30 Months

	Prenatal Surgery (N=64)	Postnatal Surgery (N=70)	Relative Risks	P value
Not Walking (%)	29	43		
Walking with assistance (%)	29	38		
Walking Independently (%)	42	21	2.01 (1.16-3.48)	0.01

Pregnancy Complications

	Prenatal Surgery (N=78)	Postnatal Surgery (N=80)	Relative Risk	P Value
Chorioamniotic Separation (%)	26	0		<0.001
Pulmonary Edema (%)	6	0		0.03
Oligohydramnios (%)	21	4	5.47(1.66-18.04)	0.001
Abruption (%)	6	0		0.03
SROM (%)	46	8	6.15(2.75-13.78)	<0.001
Spontaneous Labour (%)	38	14		<0.001
Transfusion at delivery (%)	9	1		0.03
Scar dehiscence at delivery (%)	10			

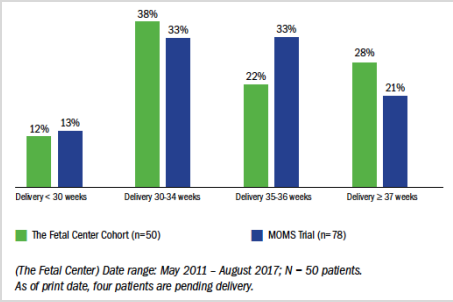
Outcomes

Fetal Surgery for Spina Bifida Repair - Summary

Fetal Surgery for Spina Bifida Repair – Summary			
	The Fetal Center Cohort (n=54)	MOMS Trial - Fetal Surgery (n=78)	MOMS Trial - Postnatal Surgery (n=80)
Gestational Age at Surgery	25.02 ± .6	23.6 ± 1.4	n/a
Gestational Age at Delivery	34.1 ± 3.5	34.1 ± 3.1	37.3 ± 1.1
Perinatal/Neonatal Demise	3 (6%)	2 (3%)	2 (2%)
VP Shunt at One Year	20/47 (43%)	31 (40%)	66 (82%)

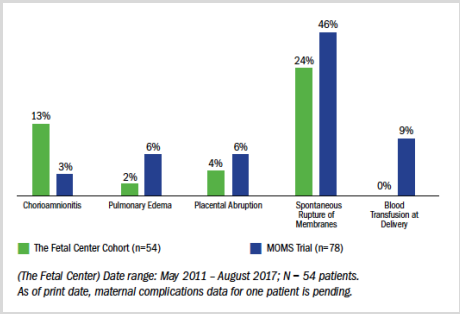
(The Fetal Center) Date range: May 2011 - August 2017; N = 54 patients. As of print date, four patients are pending delivery.

Pregnancy outcomes



(The Fetal Center) Date range: May 2011 – August 2017; N – 50 patients. As of print date, four patients are pending delivery.

Maternal outcomes



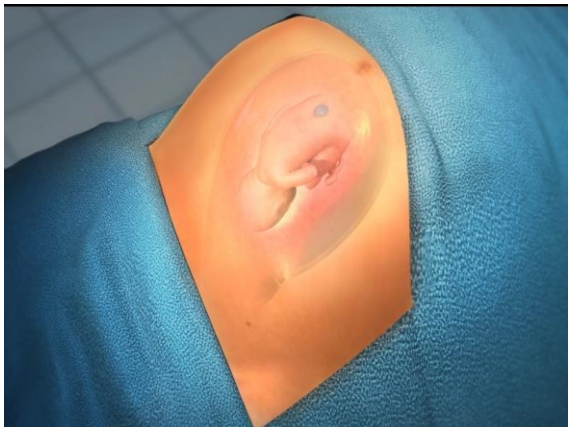
(The Fetal Center) Date range: May 2011 – August 2017; N – 54 patients. As of print date, maternal complications data for one patient is pending.

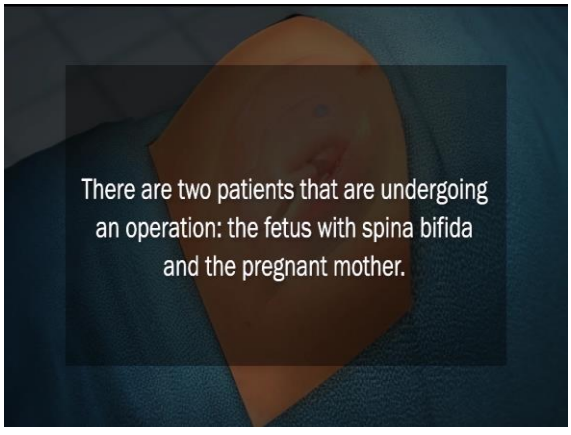
VP shunt outcomes

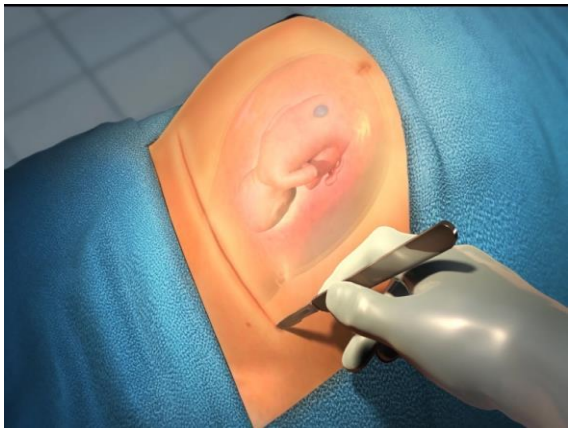
VP Shunt Rate		
	Fetal Center Cohort	MOMS Trial
VP Shunt at One Year	20/47 (43%)	31/78 (40%)

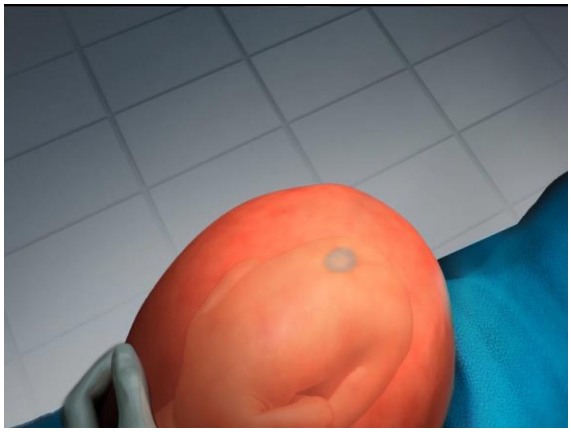
(The Fetal Center) Date range: May 2011 – August 2017. N – 47 patients, excluding neonatal demises. As of print date, four patients are pending delivery.

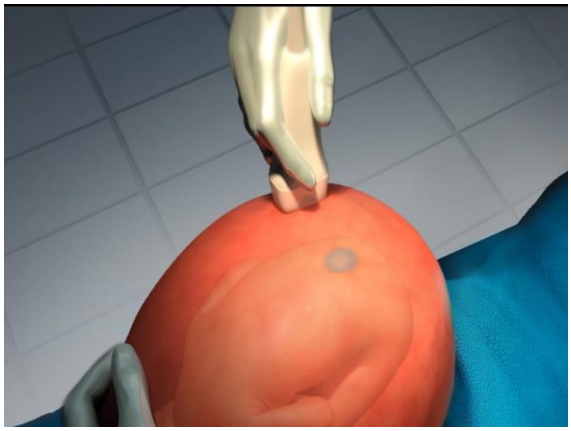
- During an 8 year period over 1,000 pregnant mothers were initially screened for the MOMs Trial.

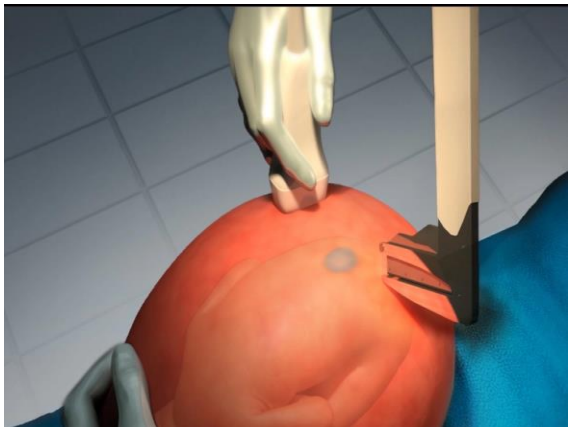


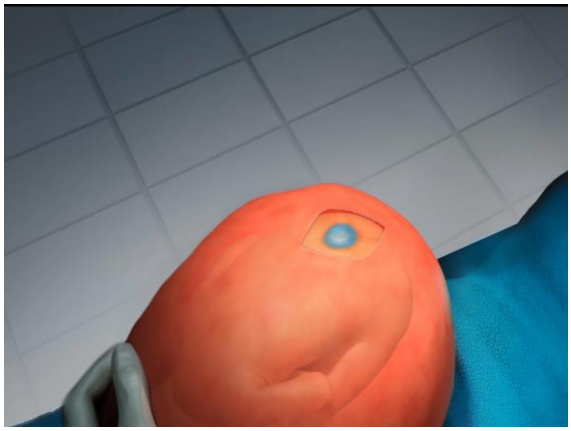


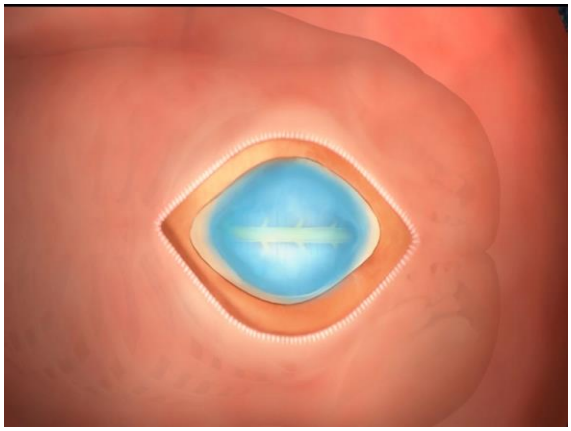


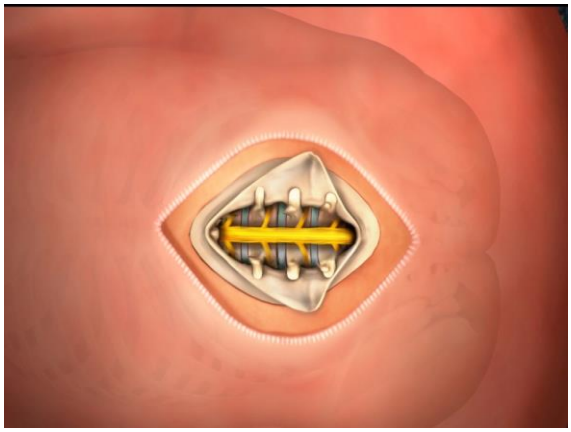


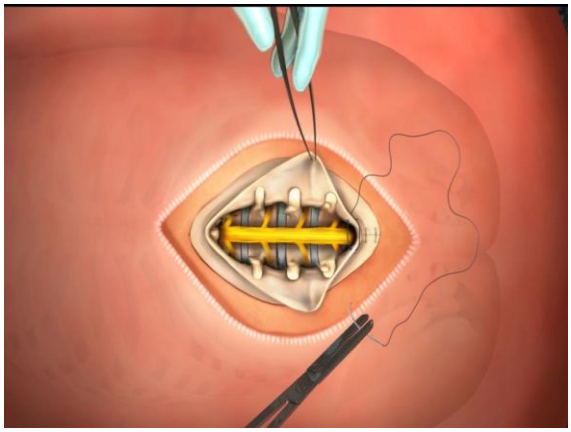


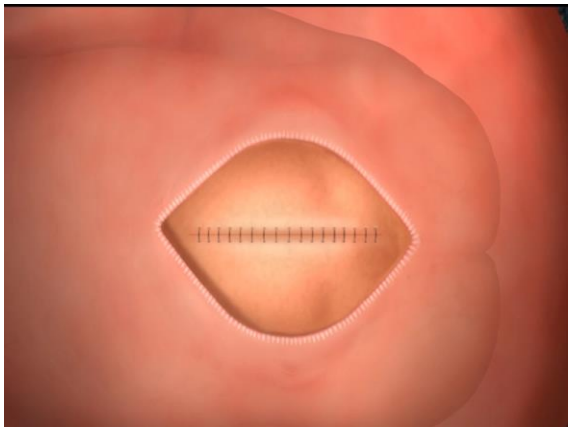


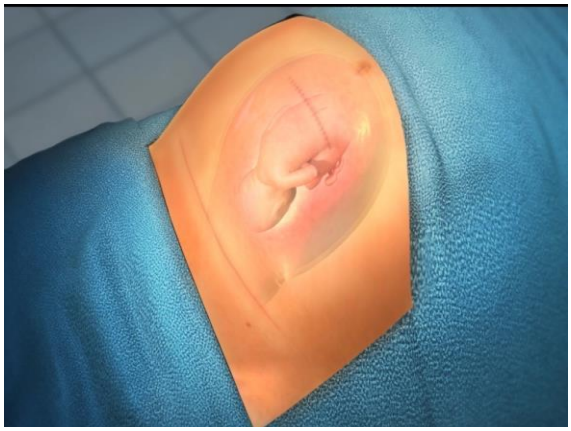


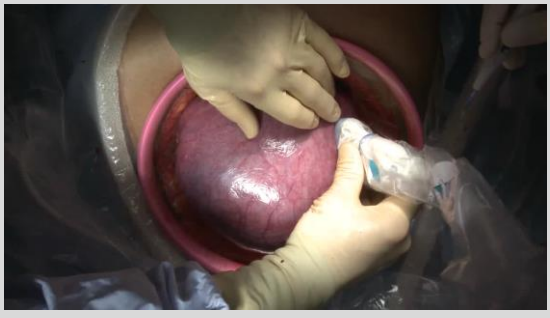












The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 550 • January 2013

Committee on Obstetric Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Maternal–Fetal Surgery for Myelomeningocele

ABSTRACT: Myelomeningocele, the most severe form of spina bifida, occurs in approximately 1 in 1,500 births in the United States. Fetuses in whom myelomeningocele is diagnosed typically are delivered at term and are treated in the early neonatal period. A recent randomized controlled trial found that fetal surgery for myelomeningocele improved a number of important outcomes, but also was associated with maternal and fetal risks. Maternal–fetal surgery is a major procedure for the woman and her fetus, and it has significant implications and complications that occur acutely, postoperatively, for the duration of the pregnancy, and in subsequent pregnancies. Therefore, it should only be offered at facilities with the expertise, multidisciplinary teams, services, and facilities to provide the intensive care required for these patients.

Recommendation

Women who meet the criteria outline in MOMs Trial should be made aware of the study findings and counseled regarding the option of maternal fetal surgery for fMMC including risks/benefits and implications to future pregnancies

CLINICAL OPINION www.AJOG.org

OBSTETRICS

Position statement on fetal myelomeningocele repair

Alan R. Cohen, MD; James Couto, MA; James I. Cummings, MD; Anthony Johnson, DO; Gerald Joseph, MD; Bruce A. Kaufman, MD; Ronald S. Litman, DO; M. Kathryn Menard, MD; Julie S. Moldenhauer, MD; Kevin C. Pringle, MB, ChB, FRACS; Marshall Z. Schwartz, MD; William O. Walker Jr, MD; Benjamin C. Warf, MD; Joseph R. Wax, MD; for the MMC Maternal-Fetal Management Task Force

- American Academy of Pediatrics
- American College of Obstetricians and Gynecologists
- American Institute of Ultrasound in Medicine
- American Pediatric Surgical Association
- American Society of Anesthesiologists
- American Society of Pediatric Neurosurgeons
- International Fetal Medicine and Surgery Society
- American Association of Neurological Surgeons/Congress of Neurological Surgeons
- Section on Pediatric Neurological Surgery
- North American Fetal Therapy Network
- Society for Maternal-Fetal Medicine
- Society of Pediatric Anesthesia
- Spina Bifida Association

Controversies

UTHealth | McGovern Medical School

Children's Memorial Hermann Hospital

Extended criteria

BMI Greater than 35

Pre-Pregnancy BMI may be greater than 35 kg/m2 but must be less than or equal to 40 kg/m2.

Structural Abnormality

Must be a minor abnormality that will not increase the risk of prematurity. Some examples include cleft lip & palate, a minor ventricular septal defect, pyelectasis, etc. A normal chromosomal microarray will also be required. This test can be done from the amniotic fluid taken during your amniocentesis.

Diabetes

Diabetic patients will require good glycemic control, for example a normal hemoglobin A1C at the start of pregnancy and compliance with insulin injections or pump therapy.

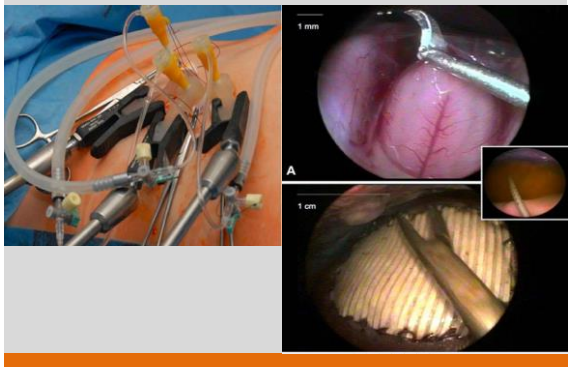
A Previous Preterm Birth

If you have a history of a previous spontaneous singleton delivery (born before 37 weeks) followed by a full term delivery.

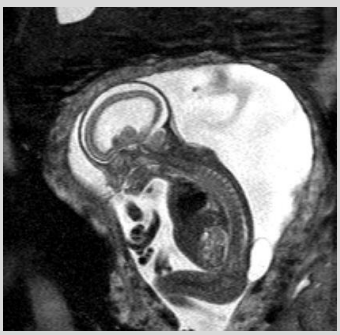
Maternal-Fetal Rh Alloimmunization

Must meet one of the following: 1. A low level of anti-red blood cell antibody that is not associated with fetal disease, specifically, anti-E < 1:4 or anti-M 2. Alloimmunization cases with a negative fetal red cell antigen status determined by amniocentesis.

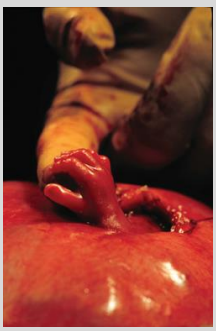
Minimally invasive fetoscopic repair

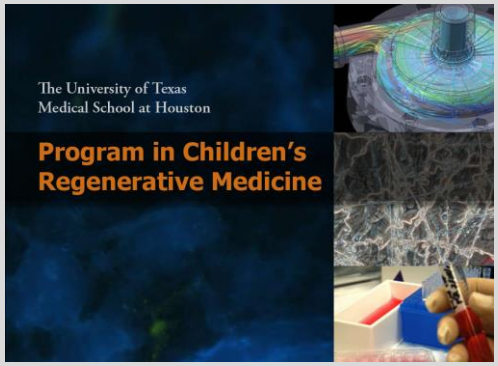


Ventricular size



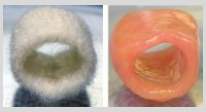
Fetal Therapy: The Future





Fetal Tissue Engineering

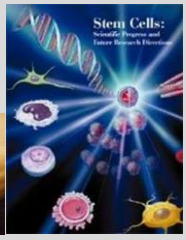
Diaphragm



Trachea

Stem Cell Therapy

- Brain injury due to congenital heart defects
- Stem cell derived cardiac patches
- Genetic disorders

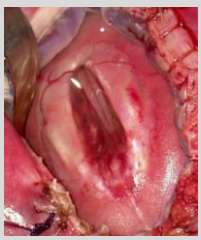


Future goals to repair

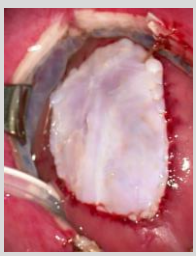
- Water tight seal of the defect to prevent hind brain herniation
- Reduce scarring and spinal cord tethering
- Repair at an earlier gestational age
- Minimally invasive spina bifida repair

Human case: HUC for in-utero repair of Spina Bifida at 23 weeks

Before Repair

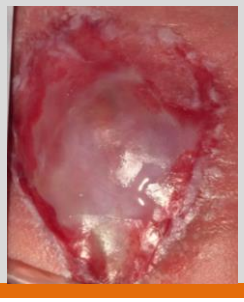


After Repair

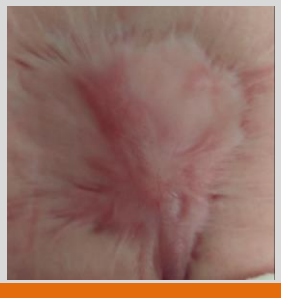


Skin defect after delivery (37 weeks)

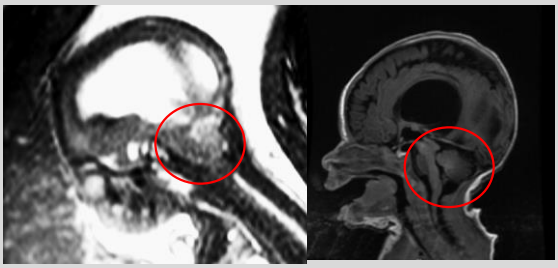
Day #1



Day # 30



Reverse of hindbrain herniation



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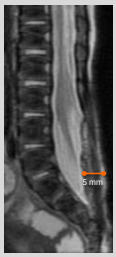
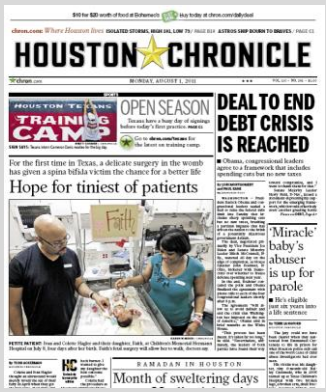
Spinal Cord and Clinical Outcomes



- Normal head size
- Normal both leg movements
- Normal bladder and bowel control

Minimal spinal cord scarring



HOUSTON CHRONICLE

OPEN SEASON

DEAL TO END DEBT CRISIS IS REACHED

For the first time in Texas, a delicate surgery in the womb has given a spina bifida victim the chance for a better life

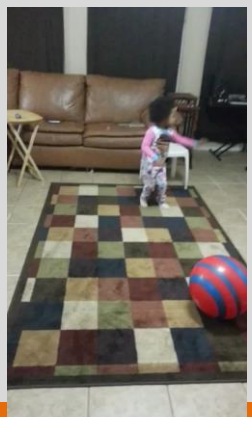
Hope for tiniest of patients

'Miracle' baby's abuser is up for parole

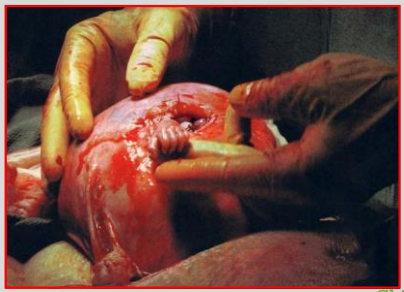
RAMADAN IN HOUSTON

Month of sweltering days

Faith at 1 year



Questions/comments



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