Fetal Intervention
When and Why, or If?

New England Obstetrics and Gynecology Society
Sturbridge, Massachusetts
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Faculty Disclosures

I have no financial interest in or affiliation with any commercial supporter to disclose.

Learning Objectives

At the conclusion of this activity participants should be able to:

1. Explain why some congenital defects are amenable to prenatal intervention and some are not
2. Explain the criteria that must be met before a therapeutic fetal procedure can be performed
3. Use the concepts of developmental sequences to predict the utility and advisability of fetal surgery

Birth Defects

- Malformation
  vs
- Disruption
  vs
- Deformation

- Can we interrupt the sequence?

Rule #6 of the House of God

There is no body cavity that can't be reached with a #14-gauge needle and a good strong arm.

The Siren's song of enabling technology

Before Doing Fetal Surgery

- Is the lesion lethal?
- Do we understand the natural history of the disorder? (*sequence*)
- Can we predict the natural history of the disorder in *this* fetus?
- Is there a prenatal intervention that will change the outcome compared to post-natal or no intervention? (*can we interrupt the sequence*?)
- Are the risks of the procedure less than the risks of NOT doing the procedure?

Birth Defects

Structural fetal defects that are lethal or lead to a sequence of other defects:

TTTS

Lower urinary tract obstruction

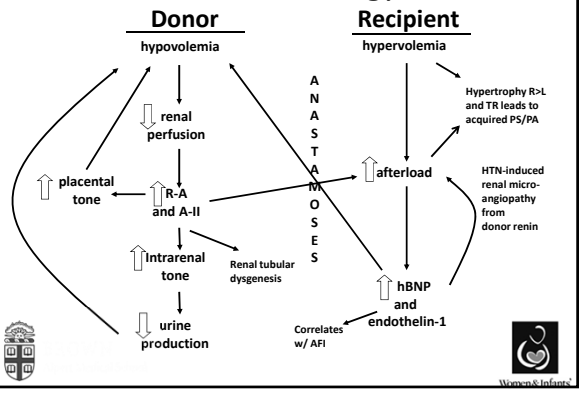
Congenital diaphragmatic hernia

Myelomeningocele

TTTS Epidemiology

- MZ twins occur 4/1000 pregnancies
- 75% will be MC/DA
- 10-15% will have severe TTTS (~1/2500 pregnancies) from unbalanced placental anastamoses
- Survival without treatment when diagnosed at < 26 weeks: ~ 30%
  - Survival comorbidities: neurologic, cardiac, ischemia/necrosis of extremities, renal cortical necrosis

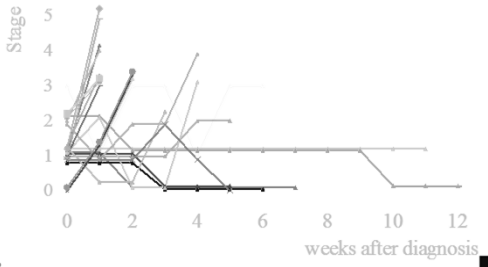
Hormonal Pathobiology of TTTS



Twin-Twin Transfusion Syndrome

- Quintero staging
  - Stage 1: AFV discordance; stomach/bladders seen
  - Stage 2: stomachs/bladders not seen
  - stage 3: abnormal Doppler flows ($AEDV_D$, TR_R)
  - Stage 4: hydrops in 1 or 2 fetuses
  - Stage 5: death of 1 or 2 fetuses
- Is there a predictable progression?

Progression of TTTS



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.

- Laser ablation versus amnioreduction
- 15 – 26 weeks
- Non-anomalous
- > 8 and < 2 cm pockets
- 1^o outcomes
  - Perinatal survival of $\geq$ 1 twin
  - Survival of $\geq$ 1 twin to 7-12 months
  - Neurologic complications at 7-12 months of age

NEJM (2004) 351;2:136-155

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- N: 172 in each group to demonstrate 15% difference
  - α 0.05; β 0.20
- Interim analysis at 72 and 144 subjects

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	Laser (n=69)	Amnioreduction (n=68)	P
Loss w/in 7 days	12%	3%	0.10
PROM w/in 7 days	6%	1%	0.37
PROM w/in 28 days	9%	9%	0.98
IUFD w/in 7 days	12%	7%	0.23

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	Laser (n=72)	Amnioreduction (n=70)	P
$\geq$ 1 survivor	76%	51%	0.002
Stage 1 or 2	86%	58%	0.007
Stage 3 or 4	66%	44%	0.07
Delivery EGA	33.3	29.0	0.003
No neurologic handicap at 6 mos of age	52%	31%	0.003

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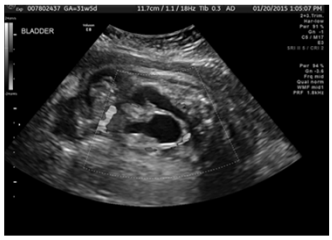
Have we met criteria?

- ✓ Is the lesion lethal?
- ✓ Do we understand the natural history of the disorder?
- ? Can we predict the natural history of the disorder in *this* fetus?
- ✓ Is there a prenatal intervention that will change the outcome compared to post-natal or no intervention?
- ✓ Are the risks of the procedure less than the risks of NOT doing the procedure?

LUTO Epidemiology

- Most commonly PUV in 1/1250 (almost exclusively) male fetuses



Antenatal Natural History of LUTO

- Early obstruction leads to back pressure into the developing nephrons, initiating dysplastic change
- Further impairment of renal function may result from vasoconstriction 2° to "inappropriate" overactivation of the renin-angiotensin system
- Degree of renal impact is related to onset, degree, and duration of obstruction
- Secondary effect of oligohydramnios on fetal lung development

Antenatal Natural History of LUTO

- Pulmonary Hypoplasia
  - Results from oligohydramnios
    - Growth and regulatory factors in AF; amniotic fluid volume maintain intra-tracheal pressure, helping to maintain intrapulmonic fluid; fetal urine an important source of proline
    - Compression of the thoracic cage
  - Decreased airway branches
  - Decreased amount of vascularity per unit lung volume, and increased muscularization of intra-acinar arteries

The Extremes

- Mild-moderate hydronephrosis with normal or near-normal amniotic fluid volume
  - No intervention is necessary
- Moderate-severe hydronephrosis, oligohydramnios, distended bladder and hyperechoic kidneys
  - No intervention will alter the outcome

Can we interrupt the sequence?

Discriminators of Good vs Poor Outcome

- Poor outcome: all "salt wasters"
- Good outcome:
  - ultrasound: non-echogenic cortex; no cortical cysts
  - Fetal urine: hypotonic

Urine analytes

- Na^+ < 100 mEq/L
- Cl^- < 90 mEq/L
- Osm < 210 mOsm/L
- Ca^{2+} < 2 mmol/L
- PO_4^- < 2 mmol/L
- β_2-μ-globulin < 2 mg/L

Glick 1995

Intervention for Posterior Urethral Valves

- UCSF Database 1981-99 (single institution)
- 36 fetuses had antenatal therapy for LUTO
  - 14 had PUV (mean 11.2 years at time of review)
  - Favorable urinary electrolytes
  - EGA 22.3 at intervention
    - bladder marsupialization, valve ablation, vesicoamniotic shunt

Holmes N et al. Pediatrics. 2001;108(1):E7

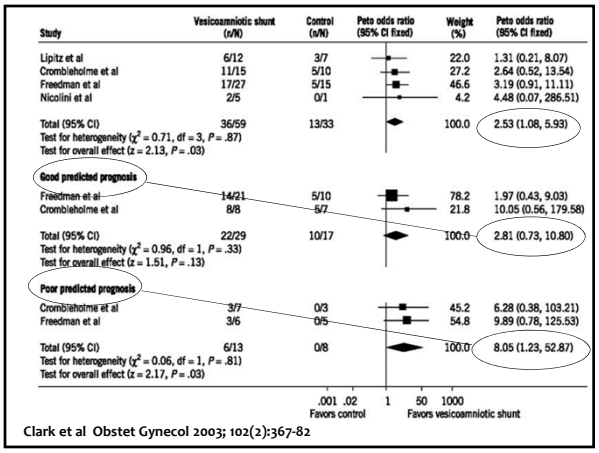
Intervention for Posterior Urethral Valves

- 8 of 14 fetuses survived – Mortality 43%
- Morbidity in survivors:
  - 5: Chronic renal disease (Abn Cr)
  - 2: Renal Transplant
  - 1: Awaiting Transplant

Intervention didn't change prognosis

Surgery for LUTO should only be offered to select fetuses with oligohydramnios and "normal" appearing kidneys

Holmes N et al. Pediatrics. 2001;108(1):E7



Clark et al Obstet Gynecol 2003; 102(2):367-82

Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial

Rachel K Morris, Gemma L Malin, Elisabeth Quinton-Jones, Lee J Middleton, Karla Hemming, Danielle Burke, Jane P Daniels, Khalid S Khan, Jon Deeks, Mark D Kilby, for the Percutaneous vesicoamniotic shunting in Lower Urinary Tract Obstruction (PLUTO) Collaborative Group

- Vesicoamnionic shunt versus conservative treatment
- Singleton male, non-anomalous other than LUTO *and* physician equipoise
- N: 75 subjects in each group
  - α 0.05; β 0.20
- 1^{o} outcome: survival to 28 days post delivery
- 2^{o} outcomes: survival at 1 and 2 years, renal function at 28d, 1 and 2 years

Lancet (2013) 382;2:1496-1506

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- 31 women randomized from 2006 – 2010
  - Trial halted due to slow enrollment

Survival Outcomes

	VAS	Conservative	p
Livebirth	12/16	12/15	>0.99
28 days	8/16	4/15	0.27
1 year	7/16	3/15	0.25
2 years	7/16	3/15	0.25
Additional cost per disability –free year	£ 43,900*		

All statistics are based on intention-to-treat

Morris RK et al. Lancet 2013; 382: 1496-506.

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Survival Outcomes

	VAS	Conservative	p
Livebirth	11/15	13/16	0.69
28 days	9/15	3/16	0.03
1 year	8/15	2/16	0.02
2 years	8/15	2/16	0.02

All statistics are based on as-treated basis

Morris RK et al. Lancet 2013; 382: 1496-506.

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Renal Function in Survivors

	VAS	Conservative
Perinatal (~ 28 days)		
Normal	2/8	0/8
ESRD	0/8	1/8
1 Year		
Normal	2/8	0/8
ESRD	0/7	0/3
2 Years		
Normal	2/7	0/3
ESRD	0/7	1/3

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Carr concludes:

- Bladder venting ***might*** improve post-natal survival but not renal function in LUTO, at cost of significant morbidity
- Restoration of normal amniotic fluid volume ***might*** enable normal fetal lung maturation ***if*** done prior to critical period, and at the cost of significant morbidity

Women & Infants'

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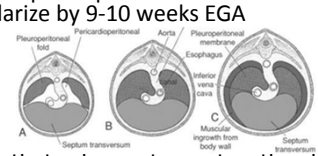
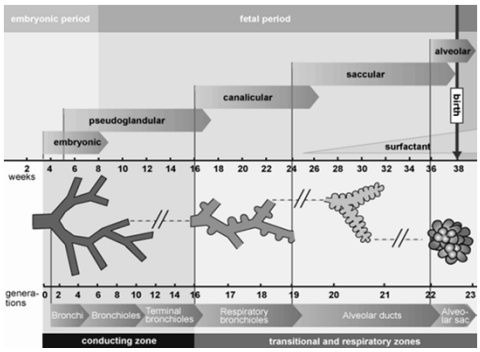
Congenital Diaphragmatic Hernia

- 1:300 – 1:5000 births
  - Including stillbirths and neonatal deaths prior to transfer to a tertiary center increases this to 1:2200
- Failure of pleuroperitoneal fold to close and muscularize by 9-10 weeks EGA



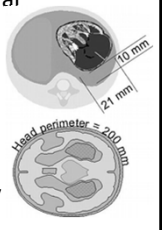
- Lacking that, when gut re-enters the abdominal cavity and undergoes 270° rotation, it herniates into thorax 2° limited abdominal space



The sequence

Assays of CDH Severity

- All proxies for inhibited parenchymal and vascular development
  - LHR – easiest
  - o/e LHR – still pretty easy
  - o/e Fetal lung volume (MRI) – not as easy
  - % liver herniation (MRI) – not as easy
  - Vascularization indices – not as easy



Predicting Severity of Pulmonary Hypoplasia in CDH

o/e LHR	Liver Position	Severity of Hypoplasia	Survival
>45%		Mild	>75%
36-45%	Down	Mild	>75%
36-45% or 26-35%	up	Moderate	30-60%
15-35%		Severe	20%
< 15%		Extreme	0%

Deprest et al. Semin Fetal Neonatal Med 2009; 14(1):8-13

Prenatal Intervention for CDH

- Open repair: neck dissection and tracheal clipping
  - 33% survival; 80% of survivors had serious neurological morbidity
- Tracheal occlusion
  - Open technique; foam plugs
  - Open technique, endoscopic access
  - Percutaneous access

Survival in CDH

	FETO n=35	No FETO n=37	*P*
Diagnosis EGA	20.8±1.8	20.6±1.5	.85
o/e LHR	0.17±0.02	0.16±0.03	.91
pPROM	12/35 (34.3%)	8/37 (21.6%)	.09
Delivery EGA	35.5±2.6	37.5±2.5	<.01
Birth weight	3036±510	3057±451	.85
Survival	19/35 (54.3%)	2/37 (5.4%)	<.01
Severe aPHTN	17/35 (48.6%)	32/37 (86.5%)	<.01

Ruano R et al. Am J Obstet Gynecol 2012;119:93-101

Fetal Surgery for CDH Trends in Clinical Experience

	Harrison (2003) n = 11	FETO consortium (2009); n = 210	South American series (2010) n = 16, 12
Surgery Criteria	LHR < 1.4; liver up	LHR < 1.0; liver up	LHR < 1.0; liver up
Device	Clip or balloon	balloon	balloon
PPROM < 34 wks	100%	25%	NR
Delivery EGA (mean)	30.8	35.3	35.6 37.0
Survival to D/C; LHR <1.4	73%		
Survival to D/C; LHR <1.0		35%	58% 42%

Harrison MR et sl. NEJM 2003;349:1916-1924
Deprest JA et al. Fetal Diagn Ther 2011;29:6-17
Ruano R et al. Fetal Diagn Ther 2011;29:64-70
Peralta CF et al. Fetal Diagn Ther 2011;29:71-77

Standardized Treatment and Outcomes in CDH

- Group 1: 2006-2007 (n = 76)
  - Gentle ventilation, delayed repair and ECMO if necessary
- Group 2: 2007 – 2009; (n = 91)
  - Peak pressures < 25 cm H_2O
  - Pre-ductal sats 85-95%; post-ductal sats > 70%
  - Arterial CO_2 45 – 60 mm Hg
  - ECMO if necessary

van den Hout et al. Fetal Diagn Ther 2011;29:55-63

Standardized Treatment and Outcomes in CDH

	N	28d mortality	Live at 28d; BPD	ECMO	Mortality after ECMO
Group 1	76	22/76 (29%)	25/53 (47%)	28/76 (37%)	18/28 (64%)
Group 2	91	8/91 (9%*)	41/83 (49%)	23/91 (25%)	7/23 (30%*)

van den Hout et al. Fetal Diagn Ther 2011;29:55-63

What the Interventions Tell Us About the Disorder

- FETO offers no benefit to not-so-bad CDH
- FETO *may* benefit severe CDH
- FETO trial

Congenital Diaphragmatic Hernia

Have we met criteria?

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MOMS Epidemiology

- Prior to folic acid supplementation, NTD's affected 1-2/1000 pregnancies
- After fortification: 31% decrease

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

N. Scott Adzick, M.D., Elizabeth A. Thom, Ph.D., Catherine Y. Spong, M.D., John W. Brock III, M.D., Pamela K. Burrows, M.S., Mark P. Johnson, M.D., Lori J. Howell, R.N., M.S., Jody A. Farrell, R.N., M.S.N., Mary E. Dabrowiak, R.N., M.S.N., Leslie N. Sutton, M.D., Nalin Gupta, M.D., Ph.D., Noel B. Tulipan, M.D., Mary E. D'Alton, M.D., and Diana L. Farmer, M.D., for the MOMS Investigators*

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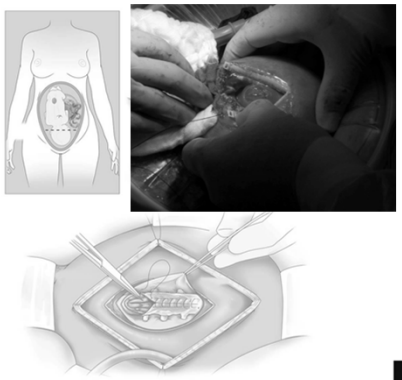
- Fetal versus conventional postnatal myelomeningocele repair
- 1^{o} outcomes:
  - A composite of fetal or neonatal death or need for shunting at 12 months
  - Composite score of the Mental Development Index of the Bayley Scales of Infant Development II and child's motor function adjusted for lesion level at 30 months
- 2^{o} outcomes: surgical and pregnancy complications and neonatal morbidity and mortality
- Randomize 100 per arm to detect 28% reduction in 1^{o} outcome

NEJM (2011) 364;11:993-1004



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MOMS Infant Outcomes at 12 months

	Prenatal Repair	Postnatal Repair	P
1º Outcome	68%	98%	< 0.001
Shunt placement	40%	82%	< 0.001
Hindbrain herniation	64%	96%	< 0.001

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MOMS Infant Outcomes at 30 months

	Prenatal Repair	Postnatal Repair	P
1º outcome score	148.6 ± 57.5	122.6 ± 57.2	0.007
Δ between motor function and anatomic level	0.58 ± 1.94	-0.69 ± 1.99	0.001
Walking independently	42%	21%	0.01

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MOMS Fetal/Neonatal Outcomes

	Prenatal Repair	Postnatal Repair	P
Birth EGA	34.1 ± 3.1	37.3 ± 1.1	< 0.001
Birth Weight	2383 ± 688	3039 ± 469	< 0.001
RDS	21%	6%	0.008

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Maternal Outcomes

	Prenatal Surgery	Postnatal Surgery	P
Pulmonary Edema	6%	0%	< 0.001
Oligohydramnios	21%	4%	0.001
Abruption	6%	0%	0.03
SROM	46%	8%	< 0.001
Transfusion at Delivery	9%	1%	0.03
Dehiscence	9%		
Complete Dehiscence	1%		

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Fetal Surgery Criteria

- Is the lesion lethal?
- Do we understand the natural history of the disorder? (*sequence*)
- Can we predict the natural history of the disorder in *this* fetus?
- Is there a prenatal intervention that will change the outcome compared to post-natal or no intervention? (*can we interrupt the sequence*?)
- Are the risks of the procedure less than the risks of *NOT* doing the procedure?

Ethical Considerations of Fetal Surgery

-We are asking people who are not sick to accept the risks of surgery.
-Even if inadvertently, we exploit a parent's desire for "the best possible" outcome for their child

Shakespeare on Fetal Surgery

For naught so vile that on the earth doth live
But to the earth some special good doth give.
Nor naught so good but, strained from that fair use
Revolts from true birth, stumbling on abuse.

Romeo and Juliet
Act 2, Scene 3