

# *Maternal-Fetal Surgery for Myelomeningocele*



# MOMS

Management of Myelomeningocele Study



# Overview

- Background
- Trial design
- Management at the clinical sites
- Results and next steps

# Background



Practices are often adopted into obstetrical management without objective evaluation, especially for high-risk patients

# *Background – Fetal Surgery*

- Fetal surgery began for lethal conditions
- Risks involve two:
  - Mom
  - Baby
- Long term risks: future pregnancies



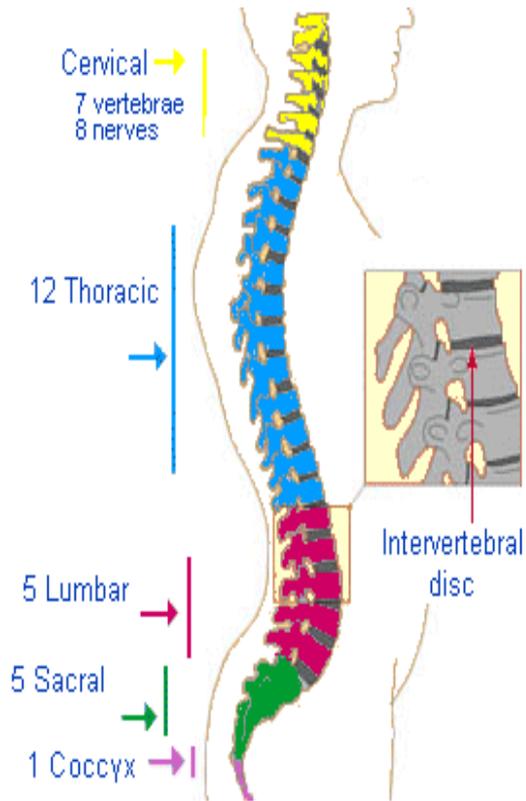
Fetal surgery for myelomeningocele  
moves beyond the typical paradigm  
- not a lethal condition

# *Background - Myelomeningocele*

- In first 28 days of pregnancy
  - Two sides of the spine join to cover the spinal cord, spinal nerves and meninges
- If it doesn't happen: birth defect with incomplete closure of spine
- Most significant/common type of **spina bifida**
  - Extrusion of the spinal cord into a fluid filled sac



# Myelomeningocele



- Most common and severe CNS congenital anomaly
- Affecting ~ 1500 fetuses in US annually
- Severity correlated with level of the spinal cord lesion
  - The higher the more severe
  - Thoracic to sacral level (lumbar most common)

# *Complications of Spina Bifida*

- Chiari II malformation – mainly hindbrain herniation (downward displacement of parts of brain into the cervical spinal canal)
  - Hydrocephalus, shunt placement to divert ventricular fluid to the peritoneum
  - Shunts can get blocked/infected
  - Brainstem malfunction, breathing, swallowing difficulty



# *Complications of Spina Bifida*

- Incompletely functioning nerves
- Muscles do not get messages from the damaged nerves
  - Varying degrees of paralysis
  - Bowel and bladder dysfunction
- Clubfoot, skeletal abnormalities
- Social, emotional issues, obesity



# *Standard of Care*

- Delivery by cesarean
- Postnatal closure of defect soon after birth
- Does not ‘cure’ spina bifida
- Most need a shunt
- Multifactorial disability – needs multidisciplinary care

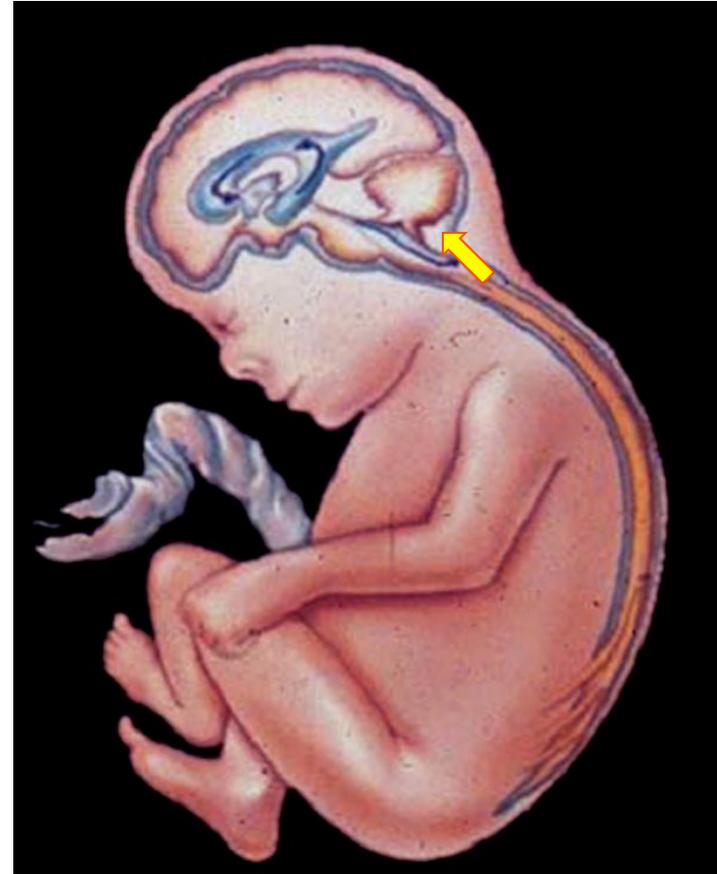


# *Fetal Surgery for Myelomeningocele*

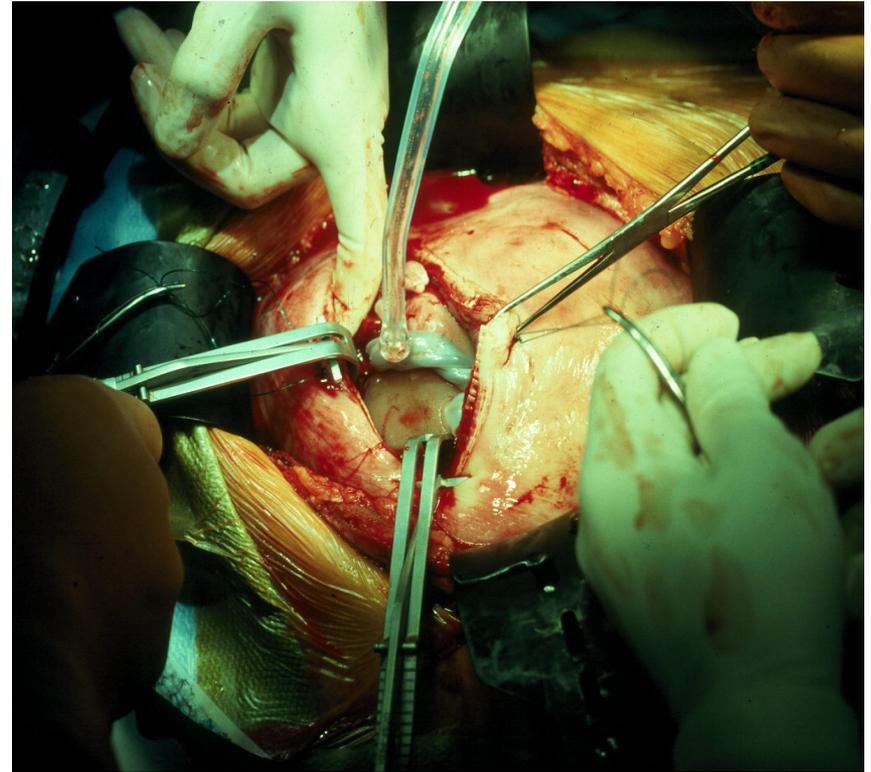
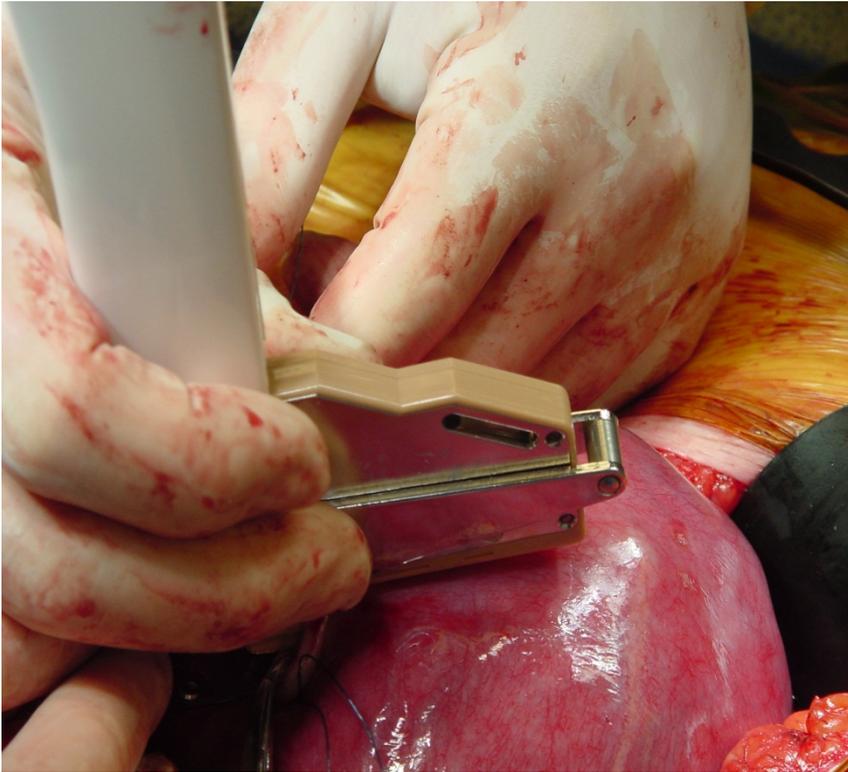
- Fetal lamb model suggested improved neuromotor function
- Prenatal closure of lesion may reduce nerve damage from exposure to amniotic fluid



# Human Fetal Myelomeningocele Repair

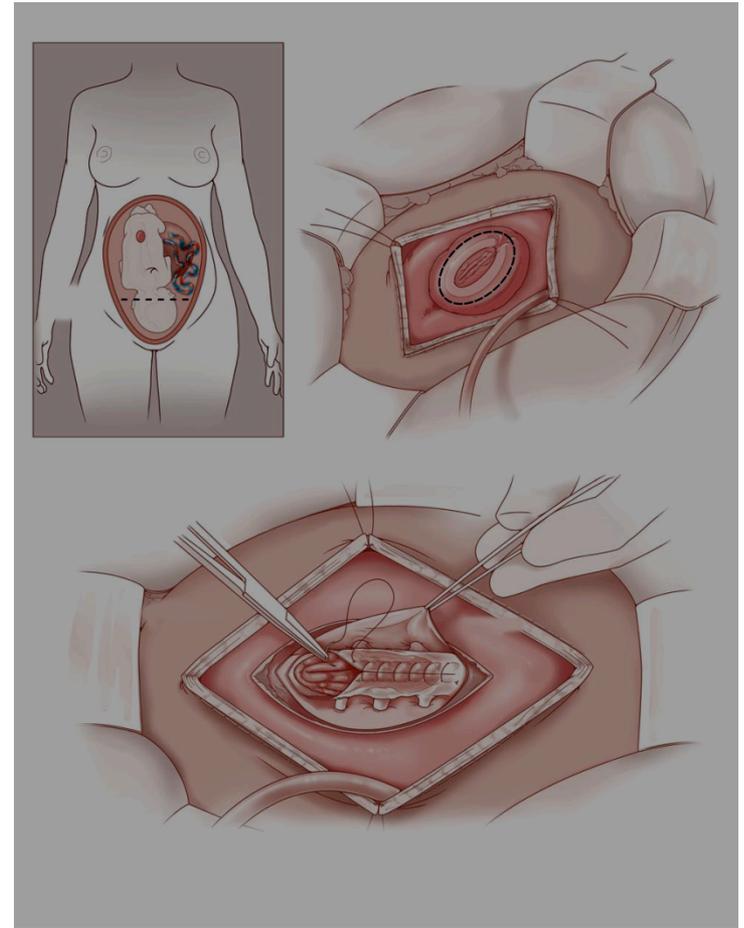


# *Prenatal Surgery: Open Hysterotomy*



# *Prenatal Surgery*

- Open hysterotomy; repair fetal lesion in utero
- By mid-2000 about 95 cases at 3 centers
- Apparent improvement in hindbrain herniation; shunting
- Conflicting results on neuromotor function



# *NICHD Workshop, July 2000*

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## *“Current Scientific, Ethical and Clinical Considerations of Maternal Fetal Surgery”*

- Encouraged name of “maternal-fetal surgery”
- Myelomeningocele surgery discussed
  - Already clinically available
  - Limited follow-up
  - Unknown if outcome better
  - Called for randomized trial

# ACOG Committee Opinion

Maternal-fetal surgery for myelomeningocele should be evaluated in a multicenter RCT



The American College of Obstetricians and Gynecologists  
*Women's Health Care Physicians*

## COMMITTEE OPINION

Number 252 – 2001

### 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.*



# *Why perform a trial?*

- Apparent benefit to prenatal surgery (hindbrain herniation/need for shunting) but...
  - Comparison with historical controls; potential confounding
  - Potential risks to mom (uterine rupture?)
  - All babies born prematurely
  - Increased risk of fetal/neonatal death
  - Short term data only / incomplete follow-up

# *Goal of the MOMS Trial*

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

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# *Development of MOMS Trial*

- Three sites (CHOP, Vanderbilt, UCSF) agreed to collaborate
- Other maternal-fetal surgery sites agreed to “no back door” policy
  - Held off developing program for myelomeningocele repair
  - No maternal-fetal surgery available in US outside of the trial



# *Trial Design Issues*

- Strong belief in benefit of prenatal surgery by some (doctors and patients) – lot of publicity
- Innovators – not used to standardization / multi-center trials
- Unmasked trial – subject to bias
- Primary outcome
  - Ventriculoperitoneal shunting practice-dependent
  - Disagreement regarding importance of shunting but neuromotor skills difficult to evaluate
  - Potential competing risk of fetal/neonatal death

# *Major Eligibility Criteria*

- Singleton
- Upper boundary of lesion at T1-S1
- Evidence of hindbrain herniation by imaging
- Gestational age 19-25 weeks
- Normal karyotype (chromosomes)
- US residency
- BMI < 35
- Low risk of preterm birth

# *Basic Study Design*

- Unmasked randomized trial
- Sample size 200
- Patients centrally screened at the Coordinating Center
- Those eligible and still interested assigned to a MOMS center
- Evaluated at MOMS center and if consenting, randomized
- Prenatal, postnatal repair & delivery at MOMS center
- 12 and 30 month follow-up

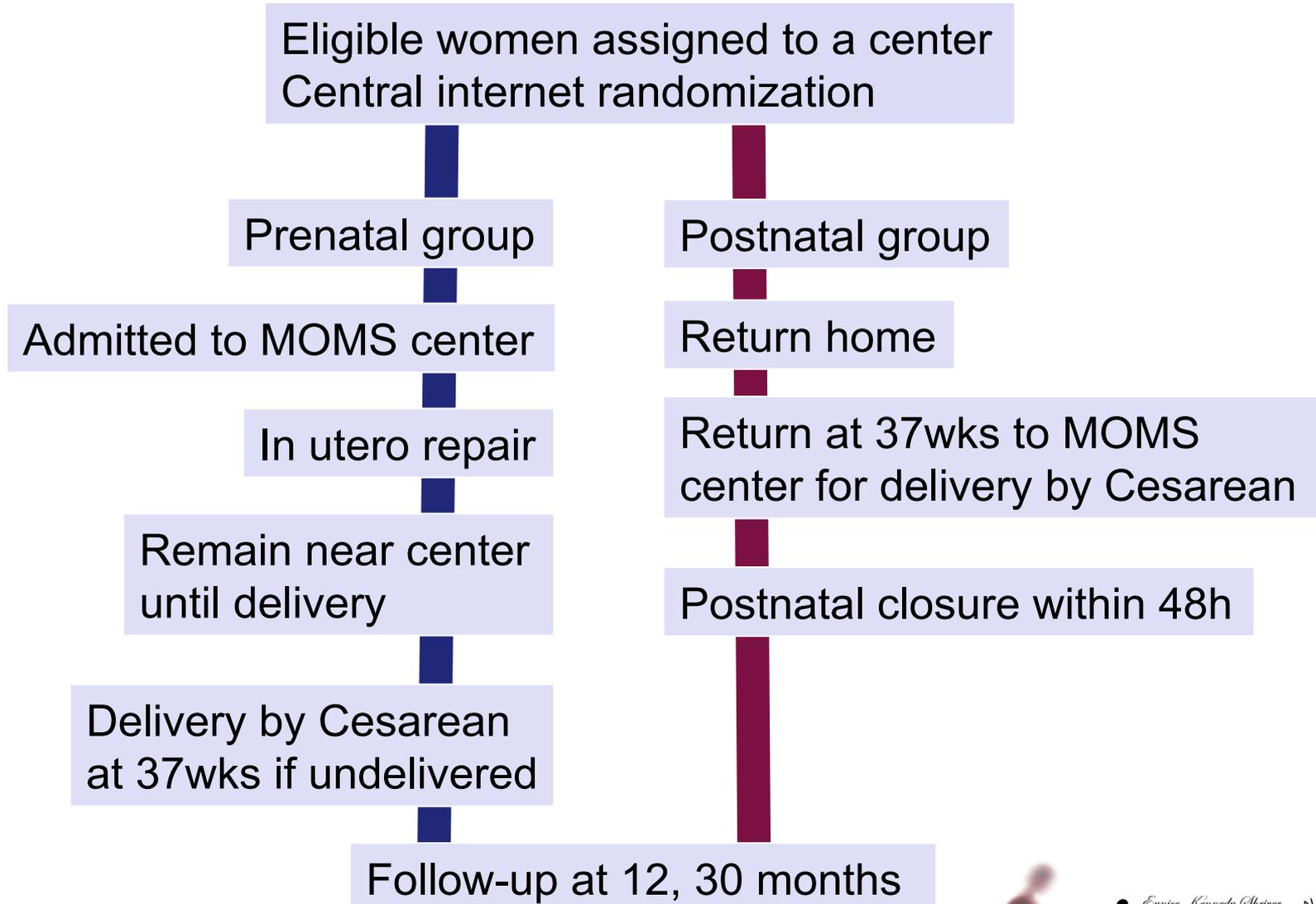
# Central Screening

- Interested patients/doctors contacted DCC
- Screening by qualified personnel (MD, genetics counselor) masked to outcome of other patients
- Counseling for all patients
  - Spina bifida information
  - Potential benefits and risks of prenatal surgery
  - Concept of randomized trial

# Referral

- Time to consider options, process information
- If patient eligible (from medical records) and could handle requirements of trial
  - Referred to one of the MOMS clinical centers
  - Assigned to center based on geography/ convenience not choice of physician

# Protocol



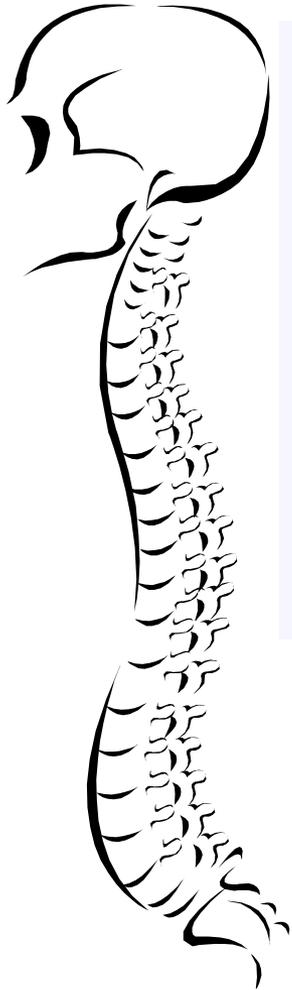
# *Primary Outcome (12 months)*

- Death or need for ventricular decompressive shunting at 12 months defined by objective criteria
  - All babies had MRI at 12 months
  - Criteria met, but no shunt – still qualifies
  - After baby born, study neurosurgeon contacted home neurosurgeon
- Independent committee of neurosurgeons (blinded to surgery group)

# *Primary Outcome (30 months)*

- Composite score (sum of ranks) of
  - Bayley Scales of Infant Development MDI and
  - Difference between the motor level and anatomic level
- Also potentially subject to bias, so
  - Evaluated by blinded independent examiners
  - Videotapes of physical exams reviewed by independent expert (motor level evaluation)

# *Difference between motor function and anatomic levels*



(Observed motor function) – (anatomic level)

Examples:

(obs S1) – (anatomic L4) = + 2 levels

(obs L2) – (anatomic L4) = - 2 levels

# *Secondary Outcomes*

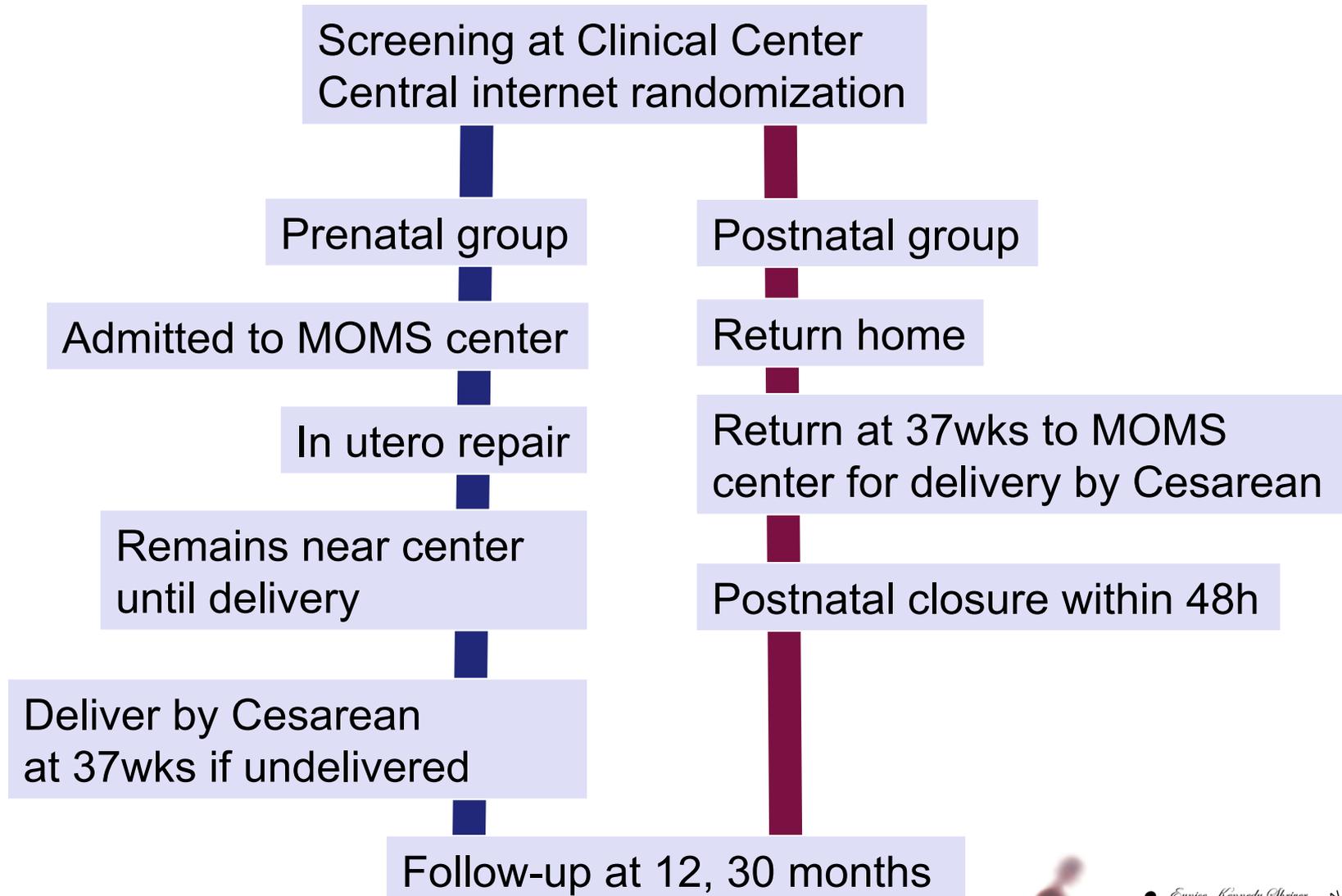
- Pregnancy and delivery complications; gestational age at delivery
- Hindbrain herniation / other brain parameters (assessed from study MRIs by independent group of radiologists)
- Bayley Scales of Infant Development and other developmental tests
- Results of physical exam – including motor function and ability to walk
- Urology outcome (assessed by independent group of pediatric urologists)

# Overview

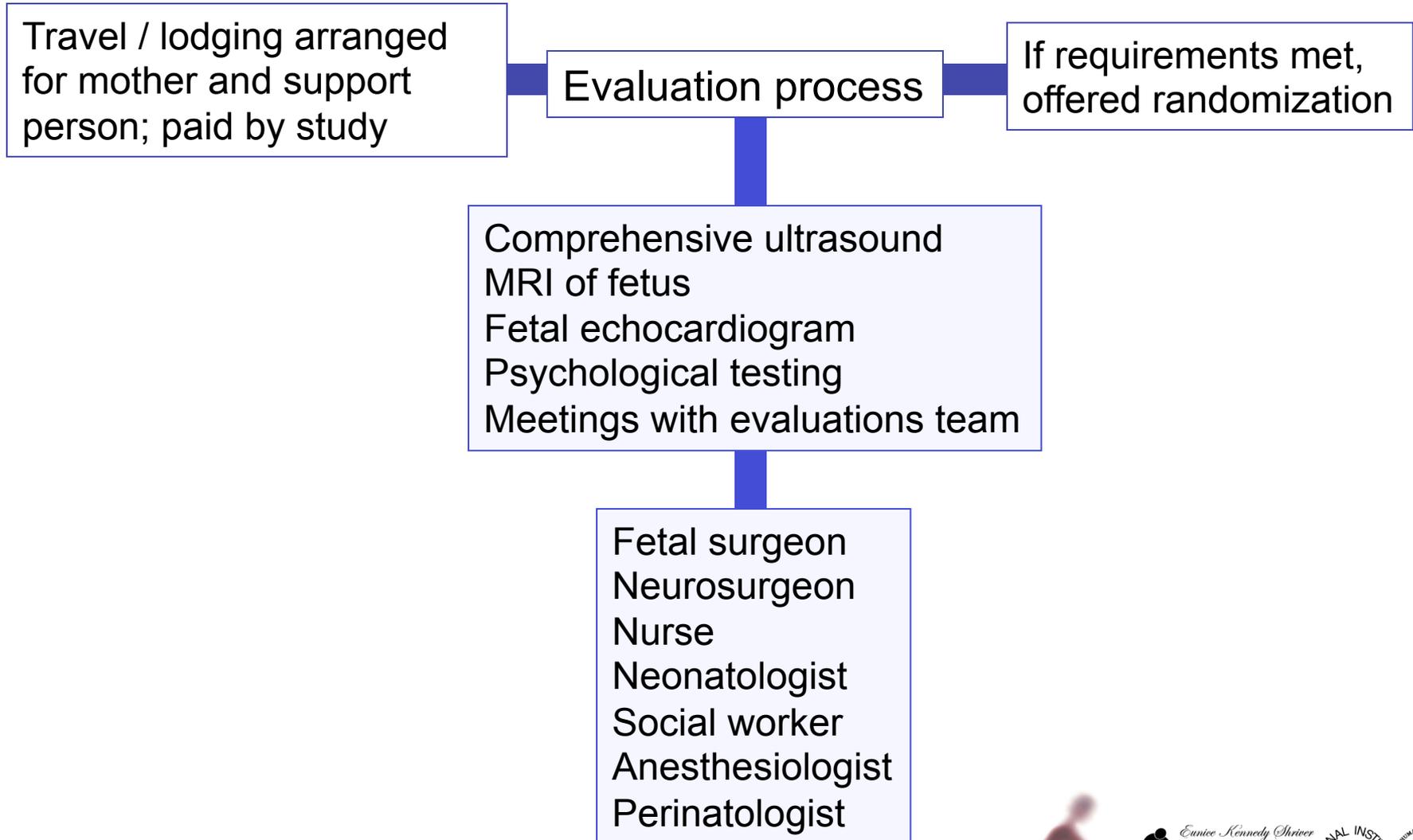
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# Protocol



# Screening at Clinical Center (2 days)



# *Fetal Rx: Judging Risks vs. Benefits*



- Risks to Mother
- Benefits/Risks to Fetus

□ ***Future Benefits to Fetal Patient***

# *Informed Consent*

- Hopes versus reality
- Confidence to say “no”
- Randomization: a blessing and a curse
- Obstacles
  - Language barriers
  - Level of education

# *Motivation to Participate*

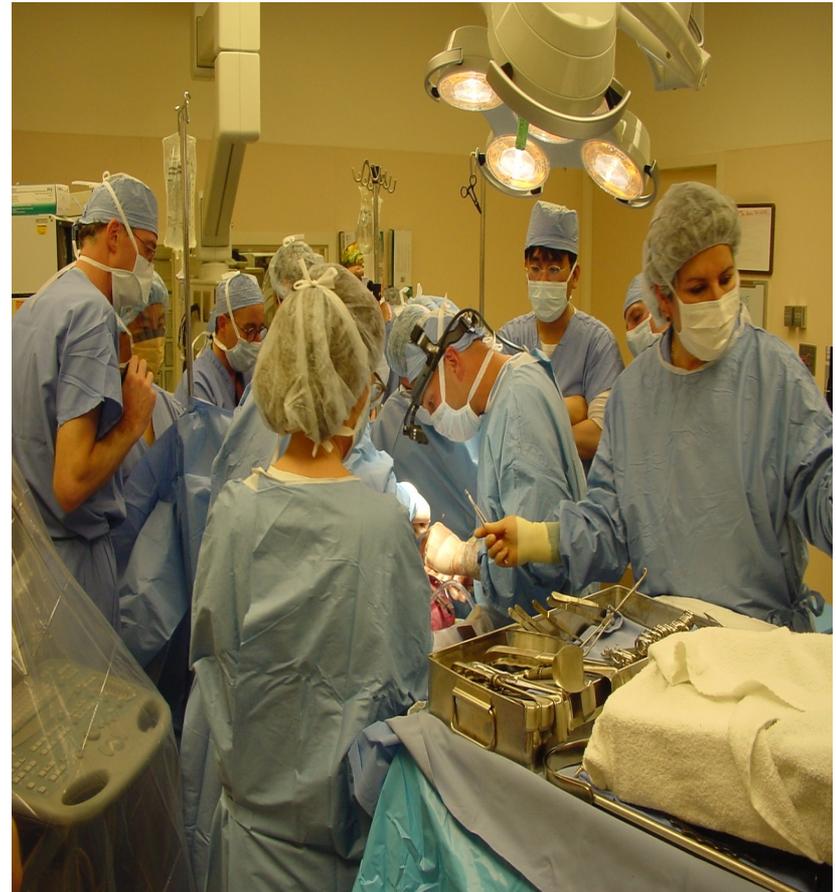
- Wanting to do everything possible for their baby
- Termination not an option
- Wanting to help other children similarly affected
- Belief and respect for medicine and medical research

# *Alternative Motivation*

- Pressure from family or partner
- Lured by the candor and kindness of team members
- Focus of attention
- Escape into a caretaking world and away from other psychosocial realities

# *Maternal Considerations*

- Stress of procedure
- Uncertainty of outcome
- Mental health issues and coping style
- Available support person
- Separation from children, spouse, work



# *Institutional Constraints*

- Limited family housing
- Time consuming process for team members

# *MOMS Coordinator Role*

- Representative on the multidisciplinary team
- Clinical understanding of the problem
- Patient advocate
- “Communicator” with all team members

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# Recruitment

- Sample size 200
- Projected timeline 18 months for recruitment (before 2<sup>nd</sup> endpoint evaluated)
- Started enrollment Feb 2003
- Data and Safety Monitoring Committee meeting in 2010 – 183 recruited

# Results

- DSMC recommendations:
  - Immediate termination of recruitment for efficacy (both boundaries crossed)
  - MOMS centers allowed to offer prenatal surgery
  - Expedite publication
- Results based on:
  - 158 patients whose children were evaluated at 12 months
  - 134 patients whose children were evaluated at 30 months

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

## 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\*



# 12 Month Primary Outcome

	<b>Prenatal N=78</b>	<b>Postnatal N=80</b>	<b>RR (95% CI)</b>	<b>P</b>
<b>Primary outcome</b>	<b>53 (68)</b>	<b>78 (98)</b>	<b>0.70 (0.58–0.84)</b>	<b>&lt;0.001</b>
<b>Related outcomes:</b>				
Actual placement of shunt	31 (40)	66 (82)	0.48 (0.36–0.64)	<0.001
Hindbrain herniation	45/70 (64%)	66/69 (96%)	0.67 (0.56–0.81)	<0.001

# 30 Month Primary Outcome

	Prenatal N=64	Postnatal N=70	P
<b>Primary outcome score</b>	<b>148.6 ± 57.5</b>	<b>122.6 ± 57.2</b>	<b>0.007</b>
<b>Components of primary outcome:</b>			
Bayley mental developmental index (MDI)	89.7 ± 14.0	87.3 ± 18.4	0.53
Difference between motor function and anatomic levels	0.58 ± 1.94	-0.69 ± 1.99	0.001
≥ 2 levels better than expected	20 (32)	8 (12)	0.002

# Secondary Outcomes (30 months)

	Prenatal	Postnatal	RR (95% CI)	P
Walking independently on exam	26 (42%)	14 (21%)	2.01 (1.16–3.48)	0.01
Bayley psychomotor developmental index	64.0±17.4	58.3±14.8		0.03
<b>Peabody Motor Scales:</b>				
Stationary score	7.4±1.1	7.0±1.2		0.03
Locomotion score	3.0±1.8	2.1±1.5		0.001
Object manipulation score	5.1±2.6	3.7±2.1		<0.001

# Maternal Outcomes

	<b>Prenatal N=78</b>	<b>Postnatal N=80</b>	<b>RR (95% CI)</b>	<b>P</b>
<b>Chorioamniotic membrane separation</b>	<b>20 (25.6)</b>	<b>0 (0.0)</b>	<b>—</b>	<b>&lt;0.001</b>
<b>Pulmonary edema</b>	<b>5 (6.4)</b>	<b>0 (0.0)</b>	<b>—</b>	<b>0.03</b>
<b>Oligohydramnios (low amniotic fluid)</b>	<b>16 (20.5)</b>	<b>3 (3.8)</b>	<b>5.47 (1.66-18.04)</b>	<b>0.001</b>
<b>Placental abruption</b>	<b>5 (6.4)</b>	<b>0 (0.0)</b>	<b>—</b>	<b>0.03</b>
<b>Blood transfusion at delivery</b>	<b>7 (9.0)</b>	<b>1 (1.3)</b>	<b>7.18 (0.90-57.01)</b>	<b>0.03</b>

# Maternal Outcome – Hysterotomy Scar

	Prenatal N=76
Intact, well-healed	49 (64.5)
Very thin	19 (25.0)
Area of dehiscence	7 (9.2)
Complete dehiscence	1 (1.3)

**35.5%**

# Fetal and Neonatal Outcomes

	Prenatal N=78	Postnatal N=80	RR (95% CI)	P
Bradycardia during repair surgery	8 (10.3)	0		0.003
Perinatal death*	2 (2.6)	2 (2.5)	1.03 (0.14-7.10)	1.00
GA at birth	34.1±3.1	37.3±1.1		<0.001
< 30 wks	10 (12.8)	0 (0.0)	15%	
30-34 weeks <b>80%</b>	26 (33.3)	4 (5.0)		
35-36 weeks	26 (33.3)	8 (10.0)		
>=37 weeks	16 (20.5)	68 (85.0)		

*Prenatal: 26wks, 23 wks*

*Postnatal: neonatal deaths with severe symptoms of Chiari II*

# *Neonatal Outcomes*

- As expected many more babies in the prenatal surgery group were born prematurely
- Significant difference in respiratory distress syndrome (RDS) 21% vs 6%
- Other morbidity rare in prenatal surgery group

# Summary



- Prenatal surgery for myelomeningocele reduces the need for a shunt or death and improves motor outcomes at 30 months but is associated with maternal and fetal risks

# Summary

- Prenatal surgery is associated with other favorable secondary outcomes:
  - Reduces hindbrain herniation at 12 months  
No evidence of herniation in 36% vs 4%
  - Doubles ability to walk without orthotics  
42% vs 21%
  - More likely to have a level of function that was two or more levels better than expected according to anatomic levels  
32% vs 12%

# Summary

- Prenatal surgery associated with maternal and fetal risks
  - Preterm birth: 80% vs 15%
  - Bradycardia
  - Oligohydramnios
  - Placental abruption
  - Transfusion at delivery
  - Uterine dehiscence at surgical site (35%)

# *Important considerations*

- Repairs were undertaken at three sites with
  - multidisciplinary teams
  - expertise in open maternal-fetal surgical cases
  - facilities to handle complications
- Specific protocol followed
  - Continuous fetal echocardiographic surveillance throughout surgery
  - Residing near center until delivery
- Implementation of this intervention should be carefully planned and monitored

# *Implementation*

- October 2011: NICHD convened MOMS Implementation meeting
  - Professional organizations, experts, insurers, governmental agencies (NIH, CDC, AHRQ, CMS)
- December 2011: MOMS Implementation Follow-up meeting convened
- Plans:
  - Consensus document on implementation underway with planned publication
  - Collaborative efforts across professional groups

# *Follow-up Study: MOMS2*



- MOMS children at 6-9 years of age
- Primary outcome:  
    Vineland Scales of Adaptive Behavior
- Visits: June 2012 - 2016

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- **Radiology Review committee:** Dorothy Bulas, M.D., Charles Fitz, M.D. and Gilbert Vezina, M.D.
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- **The Data and Safety Monitoring Committee:** George Macones, M.D., Michael Ross, M.D., Donald Stablein, Ph.D., Alessandro Ghidini, M.D., Michele Prince, MS, C.G.C., Barbara Schmidt, M.D., Antoine Khoury, M.D., Sonya Oppenheimer, M.D., John McLaughlin, M.D., Reverend Phillip Cato, Ph.D., Kellie Murphy, M.D., M.Sc., Dale Phelps, M.D., Keith Aronyk, M.D., William Hay, Jr., M.D., Mary E. Hannah, M.D., M.Sc., Jeremy Sugarman, M.D.

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# **COLLABORATORS:**

## **MOMS Centers**

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Vanderbilt University Medical Center

## **Coordinating Center**

The George Washington University Biostatistics Center

## **NICHD**

Pregnancy & Perinatology Branch

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*The fetal therapy community*

*The perinatal community*

*The Society for Maternal Fetal Medicine*

