Evolution of the Diagnosis & Treatment of CDH: Future Possibilities

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Disclosure Information

No Disclosures

Objectives

• Provide education of prenatal determination of severity of CDH

• Provide an overview of the evolution of techniques in the prenatal treatment for CDH

• Explore the future possibilities of precision medicine in the understanding and treatment of CDH
Our Early Beginnings

The Concept:

Fix simple anatomic defects which lead to disastrous physiologic consequences

Judging Risks vs. Benefits

- Risks to Mother
- Benefits/Risks to Fetus
- Future Benefits to Fetal Patient
First Animal Studies - 1981

Hysterotomy for fetal surgery & maternal safety demonstrated in a monkey model.
Clinical trials are essential to establish the place of promising new surgical therapies, before they are considered “standard” treatment.
"Liver-down" CDH

Fetal surgery works

NOT NECESSARY
Correction of Congenital Diaphragmatic Hernia in Utero, V. Initial Clinical Experience
San Francisco, California

Correction of Congenital Diaphragmatic Hernia in Utero IV. An Early Gestational Fetal Lamb Model for Pulmonary Vascular Morphometric Analysis
By N. Scott Addicks, Kristin M. Oates, Michael P. Harter, Paul Deyoe, Peter C. Glick, Alfred A. DeNarrem, and Lynne M. Rau

Correction of Congenital Diaphragmatic Hernia In Utero VII: A Prospective Trial
San Francisco, California

CAN WE PREDICT OUTCOME?
ULTRASOUND
LHR: Lung to Head Ratio

Lung area / Head circumference

The lung area contralateral to the CDH is measured at the 4-chamber view of the heart on a transverse scan of the fetal thorax.

The product is divided by the head circumference to obtain the LHR.

Gestational age <26 weeks

Tracheal obstruction works

CDH with Poor Prognosis

Reproducible
Reliable
Atraumatic
Reversible
Plug the Lung until it Grows
"Fetendo"
Minimally invasive access to the fetus

Fetoscopic Approach
European FETO Task Group

- Centers in Leuven, London, Barcelona joined in 2001
- "FETO" - Fetal Endoscopic Tracheal Occlusion
- 24 patients between April 2002 and August 2004
- Liver up, LHR=1.0 or less
- Surgery at 26 to 28 weeks gestation
- Survival
  - Neonatal = 75%
  - 28 day = 58%
  - Hospital Discharge = 50%

Observed/expected LHR

\[ \text{o/e LHR} = \frac{\text{observed LHR}}{\text{expected LHR}} \times 100 \]

- LHR increases with gestational age
- Independent of gestational age
- Quintero proposed neither LHR or o/e LHR is gestational age independent

Quantitative Lung Index (QLI)

- Quintero proposed neither LHR or o/e LHR is gestational age independent
- Right lung growth expressed as quantitative lung index
- Lung area/(HC/10)^2
- The 50th percentile of the QLI is contact at 1.0 between 16-32 weeks gestation
- Lung hypoplasia (<1st percentile) is a QLI < 0.6
Fetal Surgery vs Postnatal Care:

**BACKGROUND**

- 1980: Experimental CDH Repair
- 1986: Open CDH Repair
- 1992: Trial: Open Repair vs Postnatal Care
- 1994: Experimental Tracheal Occlusion
- 1996: Open Plug
- 1997: Open Clip
- 1999: Fetendo Clip
- 2000: Fetendo Balloon
FETAL SURGERY vs POSTNATAL CARE: A Randomized Controlled Trial for CDH

DESIGN:

Inclusion: isolated anomaly, CDH Liver up < 25 wks, LHR < 1.4
Exclusion: Failure to meet all inclusion criteria, right-sided CDH, family refuses randomization or unable to stay in SF

1° Outcome: Mortality
2° Outcome: Long-term morbidity

# Subjects Necessary N = 40

Survival 40% → 75% (α = 0.05, β = 0.2)

Conclusions

- Randomized controlled trial feasible
- Acceptance: High (24/28 randomized)
- Low Maternal/Fetal Morbidity
- PROM (64%)
- Prematurity (30.8 ± 2 weeks)
- 90 Day Survival (interim analysis)
  - Occlusion 8/11 (73%)
  - Control 10/13 (77%)
- Survival proportional to LHR
The mortality of CDH when complete case ascertainment is achieved is unaffected by new therapies. The survival rate is principally determined by the rate of antenatal termination and the incidence of associated anomalies. Reports of improved survival of CDH should be interpreted with caution, as variations in outcome are more likely to be explained by case selection artifact.

CDH New Therapies

- Delayed Surgical Repair
- ECMO (1975, Barlett, et al)
- Evolution of Mechanical Ventilators
- Evolution of Ventilation
  - Gentle Ventilation
  - Permissive Hypercapnia
  - Nitric Oxide
- EXIT to ECMO

Fetal Therapies

Natural History of untreated human fetus (1985)

Selection for Treatment
- Liver position (1987)
- Lung to Head ratio (1996)/O/E LHR (2005)

Fetal Treatment
- Open repair, 2 step (1991)
- Temporary tracheal occlusion (1994)
- Plug vs Clip (1996)
- Open vs FETO (1997)
- Randomized Trial (1999-2004)

Tracheal Occlusion To Accelerate Lung Growth – (TOTAL)

- FETO Task Group
- Tests hypothesis: does prenatal intervention increase survival and/or morbidity in isolated CDH
- Patient choice
  - Join RCT
  - Elect TO in the observational arm
- Standardized fetal, prenatal and neonatal care
- O/E LHR < 25% - Increase survival by 50%
- O/E LHR 26-45% - Increase survival and decrease BPD
- Now a European and NAFNET collaboration
What we learned from fetus

Natural History
• Hidden Mortality
• Hidden Morbidity
• Spectrum of Severity
• Prognosis \( \propto \) Lung Head Ratio (or some form of measurement)

Unsolved Problem

What we learned from trials

LESSONS
① LUNG GROWTH
② PREMATURE DELIVERY
③ Trial effect: Postnatal Care ↑
④ Morbidity ↑↑↑: Fetal = Postnatal
⑤ Trials necessary
⑥ Future: Can we collaborate?

CDH in the future

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in environment, lifestyle and genes for each person.

NIH 2015
Future Aims for CDH

1. Improving understanding of the biology of birth defects
2. Developing effective medical or surgical treatments

Known causes of CDH

- Environmental factors
  - Vitamin A deficiency Rare [Clugston et al., 2006; Pober et al., 2010]
- Chromosome aberrations
  - 15q26, 8p23.1 deletions 6.3% (2e31%) [Yu et al., 2012]
- Single gene mutations e.g.
  - STRA6, GPC3, FGZ1 <10% [Pober et al., 2010]
- Unknown
  - >70%

Surgical Innovation

CDH Recurrence
- Patch use
- Tissue Engineering
Amniotic Fluid Cell-Based Fetal Tissue Engineering

Exome Sequencing
- CDH gene mutations
  - GATA6
  - 8p23.1 Deletion
- CDH familial gene mutations
  - ZFPM2
  - Fibrillin 1 (FBN1)

International Fetal Transplantation and Immunology Society (IFETIS)
Goals:
- consensus on target diseases
- general approach for phase 1 trials
- patient/provider education and outreach

2014 - San Francisco
2015 - London
2017 - Philadelphia
Exponential Fetal Medicine

- Fetal Surgery
- Biology
- Omics
- Devices

Rare, Fatal Birth Defects — Healthy Beginnings

Stem cell/gene therapy
- thalassemia
- muscular dystrophy
- hemophilia

Pregnancy Complications
- preterm labor
- preeclampsia

Fetal Origins of Adult Disease
- diabetes
- hypertension

What we know

- CDH is a complex abnormality
- Mortality and morbidity remain high despite intensive care
- CDH can be associated with chromosomal abnormalities or genetic syndromes
- Inheritance patterns have been identified

What we know (cont.)

- Lung hypoplasia & pulmonary hypertension are the most severe sequelae
- Prenatal intervention aims to promote lung growth
- RCT are needed before TO becomes standard of care
- Genomics may assist in determination of severity of CDH