Fetal Intervention of CDH: Past, Present and Future

Hanmin Lee, MD
Director, Fetal Treatment Center, UCSF

Our Early Beginnings

The Concept:
Fix simple anatomic defects which lead to disastrous physiologic consequences

Fetal Rx: 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

\[\downarrow\]

NOT NECESSARY

LHR

- Gestational Age Dependent: Prior to 26 weeks
- 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.

FETAL SURGERY vs POSTNATAL CARE: A Randomized Controlled Trial for CDH

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

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
1º Outcome: Mortality
2º 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

European Experience/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 lung-to-head ratio (o/e LHR)

- LHR increases with gestational age
- Independent of gestational age
- o/e LHR = (observed LHR/expected LHR) x 100

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

Fetal Markers for Pulmonary Hypertension

- LPA/RPA diameter
  - RPA but not LPA larger in survivors compared to nonsurvivors (Okazaki et al. JPS 2011)
  - Prenatal MPA/contralateral PA larger in survivors with CDH and smaller MPA/contralateral PA marker for PH (Ruano et al, Ultrasound Obstet gyn 2011)
  - Fetal Ultrasound: LHR(<1.0), liver position(thoracic), stomach position(retrocardiac) correlate with delayed resolution of pulmonary hypertension (Lusk … Keller Am J Obstet Gynecol 2015)

Does Tracheal Occlusion improve PH?

- LPA larger postnatally in patients with CDH undergoing TO (Rocha…Moon-Grady 2014 Fetal Diagn Ther)
  - LV length, LV: RV ratio, LVED volume also improved after TO
- RCT: Decreased incidence of PH/Increased survival patients undergoing TO for severe CDH (Ruano et al, Ultrasound Obstet Gynecol 2012)
  - PH defined by R→L or bidirectional shunt or pre to postductal gradient >20%

Future Directions

- Use of vasodilators prenatally
- Use of corticosteroids prenatally
- Optimal timing and duration of Tracheal Occlusion
- Time limited TO device
- Intermittent TO device
- Combination therapies of above