Prenatal Predictors of Postnatal Lung Hypoplasia: MRI Assessment

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Objectives

- Identify prenatal predictors of postnatal lung and vascular hypoplasia on fetal MRI.
- Review MRI literature
- Identify MR research areas in lung hypoplasia

Lung Hypoplasia

- Autopsy lung/body weight
  - < 0.012 in GA > 28 weeks
  - < 0.015 in GA < 28 weeks
- Autopsy lung weight
  - Compared to Expected range
- Radial-alveolar count
  - Most complicated, not often used
- Clinical pulmonary insufficiency

How is pulmonary hypoplasia diagnosed?

- Pathology
  - Lung weight/Body weight (most common)
  - Pathology assessment of alveolar branching
- Clinically
  - Respiratory issues
  - Death
- **Canalicular phase**
  - Large influence of mechanical factors
  - Transpulmonary pressure (Secretion of lung fluid)
    - Efflux of 50% of lung liquid contributes to about 30% of amniotic fluid
    - Led to treatment strategies such as FETO (Fetoscopic tracheal occlusion, Deprest J)
  - Cyclic stretch, generated by fetal breathing movement

- **Saccular phase**
  - Start of surfactant production

- **Alveolar phase**
  - 85% of alveoli are formed AFTER birth

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**MRI Sequences**

- **HASTE: T2**
- **FLASH: T1**

- **HASTE**
  - Half-fourier single shot turbo spin echo
- **Chest**
  - Thymus of intermediate signal
  - 4 chamber anatomy lost due to motion
  - Aorta dark on HASTE due to flow voids
Extralobar Pulmonary Sequestration
- Markedly hyperintense to lung, intact diaphragm
- Feeding vessel from aorta seen as a flow void
- Only sequestrations had a feeding vessel

Pulmonary Hypoplasia
Fetal MRI Models
- Congenital Diaphragmatic Hernias
  - Most studied
  - Difficult model
    - Associated anomalies
    - Aneuploidy
    - Surgical condition (Complications, Technique)
- Premature Rupture of Membranes
- Urinary tract malformations

Problems using CDH model for pulmonary hypoplasia
- Pathology
  - 60-80% survival of CDH patients
  - Very few have autopsies
  - Most studies do not correlate to pathology
- Clinically
  - Death & Morbidity may occur for issues outside of pulmonary hypoplasia
    - Sepsis, Co-morbidities, Surgical complications
  - Marker for CDH morbidity early not used

Fetal MRI
- Lung Volumes
  - Validity of measurement
  - Derivation of lung weights
  - Ratio with whole body measurements
- Lung Signal Intensity
  - Ratio with liver
  - Ratio with CSF
Normal and pathological pleuroperitoneal fold formation

Assessment of fetal lung volumes and liver herniation with magnetic resonance imaging in congenital diaphragmatic hernia

Statistical significance by a $\chi^2$ test with a $p < 0.05$

Liver position in CDH is predictive of outcome

Liver assessment easier with MR

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Value of liver herniation in prediction of outcome in fetal CDH: a systematic review and meta-analysis

- 21 case series
- 407 liver up (45.4% survival)
- 303 liver down (73.9% survival) p<0.005

- Liver up as a marker for death
  - Sensitivity 73%, Specificity 54%, PPV 54%, NPV 73%
- Exists a need for further stratification

Measured liver volume in thorax and compared to lung volume and total thorax volume
- 1/8 died with Liver/Thorax <20% vs 6/7 with Liver/Thorax >20% [p<0.01]

MRI of normal and pathological fetal lung development

- 106 fetuses
  - Normal history or with abnormalities not associated with restricted lung growth
- Minimal growth of lung volumes between 140 and 175 days, at 20 and 25 GW
Difficult to predict prognosis by Quantitative Pulmonary Evaluation alone
- Increase of lung volumes is too small to evaluate differences, between weeks 20-26
- Lung volumes change with too much variance after gestational week 31

Can we simulate pathologic diagnosis of hypoplasia using Ultrasound & MRI?
- Lung volume correlates to weight
  - Use MRI to calculate lung volumes
- Ultrasound accurately calculates weight
  - Some data suggests MRI is as good if not better
  - US Weight routinely being done now

Late gestation fetal MRI-derived total lung volume predicts postnatal survival and need for ECMO support in isolated CDH
Lee TC et al. J Pediatric Surgery (2011) 46, 1165-1171
- 44 (39 left) isolated CDH
- Scanned between 32-34 weeks gestation
- ROC curve analysis showed highest accuracy for TLV of 21.2 ml

Correlation between MRI volume and weight
- 1.15 g/cm³
- 25 fetuses
- 117-3270 g
- 16 – 40 weeks
- Cavalieri grid point

Postmortem fetal organ volumetry using MRI and comparison to organ weights at conventional autopsy
Perinatal MR fetal lung volumetry and fetal LLSIR for predicting short outcome in isolated CDH and CCAM of the lung

- Technique:
  - Fetal weight by ultrasound on same day
  - Lung volume (Coakley et al.)
- 11 isolated Left CDH patients [29-36 wks]
  - 6 survivors, 5 deaths within 2 days of age
- 4 CPAM patients (Stocker 2)
- 29-40 weeks
- Ratio calculated = LV(mm³)/FBW(g)
- LLSIR calculated (Edmonton)

Perinatal MR fetal lung volumetry and fetal LLSIR for predicting short outcome in isolated CDH and CCAM of the lung

- FLV/FBW was significantly lower in neonatal death (p<0.05)
- All 5 with ratio < 6.0 died
- All 10 with ratio > 6.0 survived
- Ratio = 0.006 ml/g

Perinatal MR fetal lung volumetry and fetal LLSIR for predicting short outcome in isolated CDH and CCAM of the lung

- Calculated contralateral lung LLSIR
- Showed no difference between survivors and non-survivors

Pulmonary hypoplasia: Prediction with use of ratio of MRI-measured fetal lung volume to US-estimated body weight

- 25-39 weeks gestation
- 73 fetuses control group
  - Mean: 0.028 mL/g +/- 0.007
- 17 fetuses at risk for pulmonary hypoplasia
  - Thoracoabdominal anomalies, renal anomalies, msk dysplasia
    - 9 with hypoplasia 0.012 mL/g +/- 0.008
    - 8 without 0.023 mL/g +/- 0.009
Figure 4. Scatterplot shows relationship between FLV/FBW and gestational age.

Tanigaki S et al. Radiology 2004;232:767-772

73 fetuses at low risk
8 at high risk without hypoplasia
9 at high risk with hypoplasia

Pulmonary hypoplasia: Prediction with use of ratio of MRI-measured fetal lung volume to US-estimated body weight

- **High risk group**
  - Used cutoff of mean minus 2 SD’s, 0.014
- **Sensitivity** 8/9 (89%)
- **Specificity** 7/8 (88%)
- **PPV** 8/9 (89%)
- **NPV** 7/8 (88%)

Pulmonary Hypoplasia
Problems using body weight

- **Hydropic infant**
  - Weight inappropriately high
- **Growth restricted**
  - Weight inappropriately low

Fetal Body Volume at MR Imaging to quantify total fetal lung volume: Normal ranges

- Measured Lung volume (TFLV), liver volume (LV), and total body volume (FBV)
- Gestational age per 1st trimester ultrasound
- Correlation btw FBV and TFLV irrespective of GA or fetal growth
- No data on hypoplasia
**Observed Fetal Lung Volume**

**Expected Fetal Lung Volume**

Prenatal prognosis of CDH using MRI measurement of FLV

- 20-33 week GA, 77 fetuses with isolated CDH
- R < 25%, 19 % Survival vs 40.3% (p=0.008)

Fetal lung volume in CDH

- 30-32 weeks, 22 fetuses, 10 survivors
- R < 30%, Sensitivity =0.83, Specificity = 1 for death

Low-intensity fetal lungs on MRI may suggest the diagnosis of pulmonary hypoplasia

Why might lung signal intensity change?

- Increase in airspace and permanent secretion of fluid
- Accumulation of free protons
- Decrease of the water binding hyaluronic acid fraction
- Production of surfactant and surfactant proteins

Signal Intensity

- High variance of absolute brightness values
- Signal intensity must be compared to a reference structure
  - Amniotic fluid
  - Fetal muscle
  - CSF
  - Maternal fat
  - Liver

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Fetal lung-to-liver signal intensity ratio at MR imaging: development of a normal scale and possible role in predicting pulmonary hypoplasia in utero


Max 230/ Min 196
Avg 210/ SD 10.3
Area .51/ Pixel 39

Max 85/ Min 67
Avg 75/ SD 7.8
Area .51/ Pixel 39

Average of 3 ratios from different image/series

2.5% Lower prediction level

24 32 1.865
25 33 2.404
26 34 2.569
27 35 2.192
28 36 2.423
29 37 2.692
30 38 3.192
31 39 3.192

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Does Liver-to Lung signal intensity ratio (LLSIR) measured by fetal magnetic resonance imaging (MRI) predict the severity of pulmonary hypoplasia in congenital diaphragmatic hernia?

Hsi B, Skarsgard ED, Chari RS, Pugash D, and Bhargava R CAPS 2005

- 18 fetuses with isolated CDH
  - 16 liveborn, 4 (25%) of which survived
- LLSIR values for CDH fetuses were significantly lower than gestationally adjusted controls (p<0.05)
- LLSIR < 2.5%ile predicted mortality with a positive predictive value (PPV) of 83%.

Concerns with LLSIR

- Liver signal intensity changes more dramatically than Lung signal intensity
- Liver not in same slice as lungs
- Liver not homogeneous
- Problems could be overcome using CSF

Prediction of postnatal outcomes in congenital diaphragmatic hernia using MRI signal intensity of the fetal lung
Terui K et al. J of Perinatology (2011) 31, 269-273

- Technique:
  - Ratio of Fetal lung signal to spinal fluid signal
  - Lung volume (Coakley et al.)
- 4 deaths
  - Omphalocele
  - Coarctation

Prediction of postnatal outcomes in congenital diaphragmatic hernia using MRI signal intensity of the fetal lung
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- Technique:
  - Ratio of Fetal lung signal to spinal fluid signal
  - Total Lung volume
- Outcome

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Role of prenatal imaging in CDH

1. Predict survival
2. Predict how sick the child is at the time of admission to NICU
   - A score to compare prenatal imaging to
     - Try to minimize post-natal factors that cloud survival data
     - Requires a standardized method of neonatal assessment

SNAP-II predicts mortality among infants with CDH

SNAP-II score
- Validated risk-adjustment tool
- Neonatal illness severity score
- Calculated from 6 empirically weighted physiologic measurements made during the first 12 hours of admission to the NICU
  - Lowest blood pressure
  - Lowest temperature
  - Lowest serum pH
  - Seizures
  - PO2/FiO2 ration
  - Urine output

Present trial

Measurements
- Abnormal LLSIR
  - Both lungs have LLSIR < 2.5% le
- Lung volume
  - Both lung volumes independently < 25% of expected lung volume

Outcome
- Survival
  - Discharge from NICU alive
- SNAP-II score
  - Normal <= 17

What Goal? Prenatal counselling

- Post natal prognosis
  - Short term (Level of NICU care required, Survival to discharge)
  - Long term (Quality of life issues)
- Decision making < 25 weeks
  - Continuation of pregnancy
- Decision making regarding in utero interventions
  - 30-32 weeks
MRI Literature

- Fetus < 25 weeks
  - Presence of liver in thorax
  - Liver volume in thorax > 20%
- Fetus > 25 weeks
  - ? Some combination of volume and signal intensity

MRI predictors of pulmonary hypoplasia “in CDH”

- Presence of liver in thorax
  - Liver volume in thorax/Thoracic volume > 20%
- Total lung volume < 21.2 mL btw 32-34 weeks
- FLV/FBW < 0.014 mL/g, PV of 87%
  - < 0.006, all died
- Observed lung volume/Expected lung volume < 25%
- LLSIR < 2.5%’le, PV of 83%

Challenges

- What combination of Ultrasound, MRI, and Echocardiography parameters?
- Better stratification