Anatomical and Functional Predictors of Fetal & Neonatal Lung Hypoplasia

Yuka Yamamoto, M.D.
Fetal & Neonatal Cardiology Program
University of Alberta
Dec. 15th 2009
Outline

• Fetal Lung Development and Physiology
• Criteria of Lung Hypoplasia (LH)
• Incidence and Causes of LH
• Parameters to Predict the Severity of LH
• Clinical case (R.T.)
• Nitrofen-induced CDH Rat Study
Outline

- Fetal Lung Development and Physiology
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- Nitrofen-induced CDH Rat Study
Development of the Human Lung

- Type II pneumocytes
- Initial differentiation
- Complete mature
- Crests protrude into saccules
- Form the acinus

1986 Pringle KC
Factors for Fetal Lung Development

- **Lung growth**
  - Amniotic fluid volume
  - Intrathoracic space
  - Lung liquid volume
  - Pressure
  - Breathing movements

- **Lung maturation**
  - Glucocorticoids
  - Thyroid hormones
Outline

• Fetal Lung Development and Physiology
• **Criteria of Lung Hypoplasia (LH)**
• Incidence and Causes of LH
• Parameters to Predict the Severity of LH
• Case Report
• Nitrofen-induced CDH Rat Study
Lung Hypoplasia (LH): Clinical Features

- Immediate onset of severe respiratory insufficiency after birth
- Small lung capacity
- Required high ventilatory pressures in the absence of airway obstruction or atelectasis
Pathological Criteria of LH

< 28 weeks
Lung / Body weight < 0.015

≥ 28 weeks
Lung / Body weight <

1981 & 1982 Wigglesworth and Des
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• Criteria of Lung Hypoplasia (LH)
• **Incidence and Causes of LH**
• Parameters to Predict the Severity of LH
• Clinical case (R.T.)
• Nitrofen-induced CDH Rat Study
LH: Incidence

- 9-11/ 10,000 live births
- Perinatal mortality: 70% (55- 100%)
  - Preterm Premature Rupture of Membranes (pPROM): 10% of all pregnancies (5-45% with world-wide reports)
    - 90% in labour
    - 10% prolonged pPROM
    - LH 12.9% in pPROM(15- 28w); 2000 Hung Winn.
  - Congenital Diaphragmatic Hernia (CDH):
    - 2.7 in 10,000 live birth; 2007 D. Gallot et al.
LH: Etiology

- Oligohydraminos based
  - Renal: bilateral renal agenesis
  - Non-renal: pPROM
- Intrathoracic masses (CDH, Congenital Cystic Adenomatoid Malformation; CCAM)
- Renal oligohydraminos
- Skeletal malformation
- Neuromuscular and central nervous system anomalies
- Pleural effusions
- Cardiac lesions
- Abdominal wall defects
- Primary LH syndromes associated with LH

2000 J. Laudy and J. Wladimiroff
Preterm Premature Rupture of Membranes (pPROM)

Perinatal mortality in pregnancies with pPROM

- Gestational age at rupture of membranes
- Latency period
- Volume of amniotic fluid

- Independent factors to predict LH

2000 H. Winn et al.
Congenital Diaphragmatic Hernia (CDH)
Outline

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- Incidence and Causes of LH
- Parameters to Predict the Severity of LH
- Clinical case (R.T.)
- Nitrofen-induced CDH Rat Study
Parameters to Predict Severity of LH

- Lung Volume Estimation
- Branch Pulmonary Artery (PA) Diameters
- PA Doppler Flow:
  - Acceleration Time/ Ejection Time (AT/ET ratio)
  - Peak Early Diastolic Reverse Flow (PEDRF)
  - Pulsatility Index (PI)
- 3D Lung Volume Measurement (echo)
- MRI:
  - Lung-to-Liver Signal Intensity Ratio (LLSIR)
  - Lung volume
2D Lung Volume Estimation

- TA/ HA (thoracic / heart area) ratio
- TC/ AC (thoracic/abdominal circumference) ratio
- CC/ TC (cardiac/ thoracic circumference) ratio
- (TA- HA)/ TA ratio

Both the ellipse and diameter methods of measuring cardiothoracic ratio are reproducible.

2006 A. Awadh et al.
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td><strong>TA/HA:</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1997 Yoshimura</td>
<td>68.8</td>
<td>100</td>
<td>100</td>
<td>85.7</td>
</tr>
<tr>
<td>2007 F. Gerards</td>
<td>100</td>
<td>58</td>
<td>54</td>
<td>100</td>
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<tr>
<td><strong>TC/AC:</strong></td>
<td></td>
<td></td>
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<tr>
<td>1996 Yoshimura</td>
<td>90.5</td>
<td>90</td>
<td>86.4</td>
<td>93</td>
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<tr>
<td>2002 J. Laudy</td>
<td>69</td>
<td>71</td>
<td>61</td>
<td>77</td>
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<tr>
<td>2007 F. Gerards</td>
<td>50</td>
<td>75</td>
<td>50</td>
<td>75</td>
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<tr>
<td><strong>CC/TC:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002 J. Laudy</td>
<td>76</td>
<td>50</td>
<td>52</td>
<td>75</td>
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<tr>
<td><strong>(TA-HA)/ TA:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996 Yoshimura</td>
<td>68.8</td>
<td>96.7</td>
<td>91.7</td>
<td>85.3</td>
</tr>
</tbody>
</table>
Observed/ Expected Lung area to Head circumference (O/E LHR)

Sensitivity 46%, False positive rate 10%


2007 J. Jani et al.

Sensitivity 46%, False positive rate 10%
3D Lung Volume Measurements

Sensitivity: 83%, Specificity: 100%
PPV 100% NPV 92%

2007 F. Gerards et al.
Pulmonary Artery
Pulmonary Artery
Pulmonary Artery

Good correlation with lung weight!

2002 J. Sokol et al.
PA Diameters in CDH

Ipsilateral branch PA diameter results in progressive hypoplasia advanced gestation.

2001 J. Sokol et al.
Ipsilateral PA Diameter predictive of respiratory morbidity

<table>
<thead>
<tr>
<th></th>
<th>Duration on oxygen</th>
<th>Duration of ventilation</th>
<th>Length of stay</th>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td><strong>LPA(ga)</strong></td>
<td>-0.69</td>
<td>0.009*</td>
<td>-0.68</td>
</tr>
<tr>
<td><strong>RPA(ga)</strong></td>
<td>-0.43</td>
<td>0.139</td>
<td>-0.41</td>
</tr>
</tbody>
</table>

2006 Sokol et al.

Ipsilateral PA Diameter predictive of respiratory morbidity
Branch PA Doppler Flow

Peak Systolic Velocity (PSV)

Peak Diastolic Velocity (PDV)

Peak Early Diastolic Reverse Flow (PEDRF)

Pulsatility Index (PI) = (PSV - PDV)/ Mean Velocity
Branch PA Doppler Flow

Proximal

Middle

Distal

2000 & 2002 J. Laudy
PA Doppler Depending on the Part

Middle branch

Distal branch

There are Inter-pulmonary (proximal, middle, distal) differences in arterial blood flow velocity parameters

2000 J. Laudy
Acceleration time / Ejection time (AT/ET) ratio

In pulmonary hypertension
- Rapid acceleration
- Short acceleration time

AT in adults highly correlates with mean pulmonary artery pressure.

1983 Circulation, A. Kitabatake et al.
AT/ET ratio by Fuku et al. 2003 Am J Onstet Gynecol.

Normal range of LPA (n=75)

Outcome of suspected LH (n=17)

AT/ET ratio correlates with survival in fetuses at risk for lung hypoplasia
Peak Early Diastolic Reverse Flow (PEDRF)

Higher PEDRF is seen with higher pulmonary vascular resistance.
Peak early diastolic reverse flow (PEDRF)

By O. Moreno- Alvarez et al. 2008 Ultrasound Obstet Gynecol

PEDRF has significant relationship with O/E LHR

PEDRF has significant relationship with O/E LHR
Maternal Hyperoxygenation Test

Reactive: Decrease in Pulsatility Index (PI) > 20%

Non reactive: Decrease in PI < 20%

2002 R. Broth et al.
Maternal Hyperoxygenation Test

n = 29

Non-Reactive
n = 15
- Lethal LH (+) n = 12
- Lethal LH (-) n = 3

Reactive
n = 14
- Lethal LH (+) n = 1
- Lethal LH (-) n = 13

Sensitivity: 92%, Specificity: 82%

2002 R. Broth et al.
Maternal Hyperoxygenation Test

1998 Circulation, J. Rasanen

20- 26 weeks

Room air

Before During After

60% oxygen

Before During After

31- 36 weeks

Room air

Before During After

60% oxygen

Before During After
Fetal Lung-to-Liver Signal Intensity Ratio (LLSIR) at MRI
LLSIR by L. Brewerton et al. 2005

Hypoplastic lungs

At more than 25 weeks, all LLSIRs for the LH are outside the lower bound.

LLSIR is high potential predictor of severe LH after 25 weeks of gestation.
Outline

• Fetal lung development and physiology
• Criteria of Lung Hypoplasia (LH)
• LH causes
• Parameters to predict the severity of LH
• Clinical case
• Nitrofen-induced CDH rat study
Clinical case

- 37 y.o. G3 P1
- Medical history: asthma
- Obstetrics history: ectopic pregnancy
- Family history: N/A

- Natural pregnancy
- 21 weeks: pPROM with no sign of chorioamnionitis
- Antenatal steroids at 24 weeks
- Antibiotics: amoxicillin, erythromycin
pPROM at 31 weeks
pPROM at 33 weeks

Branch PA Diameters

RPA = 0.43 cm
LPA = 0.44 cm
Room Air

AT/ET = 0.18
PEDRF = 14 cm/s

AT/ET = 0.13
PEDRF = 11 cm/s
PI = 2.17

Hyperoxygenation

AT/ET = 0.15
PEDRF = 18 cm/s
PI = 3.7

LPA

AT/ET = 0.15
PEDRF = 14 cm/s
PI = 2.5

PI = 34% reduction
Clinical Report: Outcome

- 34w2d
- C/S due to the risk of chorioamnionitis
- 2010g, 44.5cm boy
- Apgar scores 3/6, UA pH= 7.28
- Brief ventilatory support with CPAP
- No positive results from infection screening
- Discharge: 4 days later.

Good lung maturity!
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Nitrofen–induced CDH Animal Model

Sprague-Dawley rat

E 9.5 day
- Control
- 100mg Nitrofen

E 11.5-20.5 day
- Control
- Sildenafil (100mg/kg/d)

20.5 day:
- Echo examination (fetal PAs) & Hyperoxygenation test
- Up to 50%
- Evaluation of lung morphology
- C/S
Upcoming Research in Edmonton

- Prospective study
- 130 patients
  - 60 lung hypoplasia (CDH, pPROM, CCAM, renal agenesis)
  - 70 control
- Investigate the best predictor of lung hypoplasia severity using echo imaging, maternal hyperoxia testing and fetal MRI assessment
Thank you very much!

For great support
Dr. Lisa Hornberger
Dr. Lisa Howley
Dr. Bernard Thebaud
Dr. Venu Jain
Dr. Chari Radha
Dr. Ravi Bhargava

Research Nurse: Winnie Savard

Founding: Juntendo University School of Medicine
Lung volume estimation

- TA/HA ratio
- (TA-HA)/TA ratio
- CC/TC ratio
- TC/AC ratio

Lung area to Head circumference (LHR)

1996 A. Metkus et al.
55 fetuses with CDH diagnosed

<table>
<thead>
<tr>
<th>No. of Fetuses</th>
<th>ECMO</th>
<th>Mean AFPD (cm)</th>
<th>LHR</th>
<th>Abdominal Circumference (cm)</th>
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<tbody>
<tr>
<td>Survivors</td>
<td>36</td>
<td>5.9 ± 2.5</td>
<td>1.33 ± 0.50</td>
<td>22.4 ± 7.7</td>
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<tr>
<td>Nonsurvivors</td>
<td>19</td>
<td>6.1 ± 2.3</td>
<td>0.87 ± 0.32</td>
<td>19.7 ± 3.3</td>
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<tr>
<td><em>p</em> value</td>
<td>NG</td>
<td>NG</td>
<td>&lt;.0001</td>
<td>NG</td>
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<table>
<thead>
<tr>
<th>LHR</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.6</td>
<td>0% (0 of 5)</td>
</tr>
<tr>
<td>&gt; 0.6 and ≤ 1.35</td>
<td>57% (16 of 28)</td>
</tr>
<tr>
<td>&gt; 1.35</td>
<td>100% (5 of 5)</td>
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</table>
Lung area to Head circumference (LHR)

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Percentage with intrathoracic liver herniation</th>
<th>Gestational age at LHR measurement (weeks)</th>
<th>LHR cut-off</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td>Metkus et al. 1996</td>
<td>38</td>
<td>≥ 80</td>
<td>≤ 25</td>
<td>&lt; 0.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6–1.35</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 1.35</td>
<td>100</td>
</tr>
<tr>
<td>Lipshutz et al. 1997</td>
<td>15</td>
<td>Not given</td>
<td>24–26</td>
<td>&lt; 1.0</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–1.4</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 1.4</td>
<td>100</td>
</tr>
<tr>
<td>Harrison et al. 1998</td>
<td>13</td>
<td>100</td>
<td>20</td>
<td>&lt; 1.0</td>
<td>20</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>1.0–1.4</td>
<td>57</td>
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<tr>
<td>Flake et al. 2000</td>
<td>47</td>
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<td>23–25</td>
<td>&lt; 1.0</td>
<td>0</td>
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<td>1–1.4</td>
<td>56</td>
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<td></td>
<td></td>
<td></td>
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<td>≥ 1.4</td>
<td>85</td>
</tr>
<tr>
<td>Sbragia et al. 2000</td>
<td>20</td>
<td>0</td>
<td>16–26</td>
<td>&lt; 1.4</td>
<td>89</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>≥ 1.4</td>
<td>73</td>
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<td></td>
<td></td>
<td></td>
<td>1–1.4</td>
<td>38</td>
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<tr>
<td>Laudy et al. 2003</td>
<td>21</td>
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<td>100</td>
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<td>≥ 1.4</td>
<td>67</td>
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<td>1.0–1.4</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 1.4</td>
<td>40</td>
</tr>
<tr>
<td>Heling et al. 2005</td>
<td>22</td>
<td>64</td>
<td>16–38</td>
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<td>0</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>1.0–1.4</td>
<td>60</td>
</tr>
</tbody>
</table>

2006 J. Jani et al.
Lung area to Head circumference (LHR)

184 CDH cases between 22 to 28 weeks

<table>
<thead>
<tr>
<th>LHR</th>
<th>Yes (Group A)</th>
<th>No (Group B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Survival (n (%))</td>
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<tr>
<td>0.4–0.5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0.6–0.7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>19</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>1.0–1.1</td>
<td>23</td>
<td>14 (60.9)</td>
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<tr>
<td>1.2–1.3</td>
<td>19</td>
<td>13 (68.4)</td>
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<tr>
<td>1.4–1.5</td>
<td>11</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>≥ 1.6</td>
<td>6</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>43 (50.0)</td>
</tr>
</tbody>
</table>

2006 J. Jani et al.

Poor prognosis = LHR < 1.0 with liver herniation
Observed LHR/ Expected LHR (O/E LHR)

Normal fetus

2005 C. F. A. Peralta et al., 2007 J. Jani et al.
LHR & O/E LHR in CDH

Sensitivity 46%, False positive rate 10%

2007 J. Jani et al
PA Diameters in Normal Fetus

LPA

RPA

2007 S. Katayama
PA diameters in CDH

PA diameter may be useful to predict **perinatal death** but not LH itself.

---

**Table 1** Prenatal PA diameters and neonatal outcome in cases of CDH

<table>
<thead>
<tr>
<th>Perinatal outcome</th>
<th>Neonatal PAH *</th>
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<tbody>
<tr>
<td></td>
<td>Present (n = 13)</td>
</tr>
<tr>
<td>Perinatal death (n = 11)</td>
<td></td>
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<tr>
<td>Main PA diameters</td>
<td>0.76 (0.51-1.13)</td>
</tr>
<tr>
<td>Contralateral PA diameters</td>
<td>0.68 (0.49-0.86)</td>
</tr>
<tr>
<td>Ipsilateral PA diameters</td>
<td>0.41 (0.21-0.65)</td>
</tr>
</tbody>
</table>

Values are reported as median (range).

* One case was excluded because of death of the fetus, in which it was not possible to evaluate the presence of pulmonary arterial hypertension clinically.

2008 R. Ruano et al.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Fetal age at time of study (wk)</th>
<th>Diagnosis</th>
<th>Reactivity (% change)</th>
<th>Outcome</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>Oligohydramnios</td>
<td>No (7%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Information not available</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>CDH</td>
<td>No (4%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>CCAM</td>
<td>No (6%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Extracorporeal membrane oxygenation, mechanical ventilation with oxygen requirements ≥ 40%, died after 85 d</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>CDH</td>
<td>No (3%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Autopsy</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>Oligohydramnios</td>
<td>No (0%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Autopsy</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>Pleural effusions</td>
<td>No (1%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Oscillator with 100% oxygen requirement, died after 18 d</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>Skeletal dysplasia</td>
<td>No (4%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Died in delivery room</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>Oligohydramnios</td>
<td>No (3%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Oscillator with 95% oxygen requirement, died after 2 d</td>
</tr>
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<td>9</td>
<td>31</td>
<td>Twin-twin transfusion syndrome</td>
<td>No (8%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Autopsy</td>
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<td>10</td>
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<td>No (8%)</td>
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<td>Autopsy</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>Oligohydramnios</td>
<td>No (3%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td>Autopsy</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>Oligohydramnios</td>
<td>No (3%)</td>
<td>Live born</td>
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</tr>
<tr>
<td>13</td>
<td>36</td>
<td>CDH/omphalocele</td>
<td>No (5%)</td>
<td>Nonlethal pulmonary hypoplasia</td>
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</tr>
<tr>
<td>14</td>
<td>35</td>
<td>CDH</td>
<td>No (3%)</td>
<td>Nonlethal pulmonary hypoplasia</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>CCAM</td>
<td>Yes (33%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>32</td>
<td>CDH</td>
<td>Yes (43%)</td>
<td>Live born</td>
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</tr>
<tr>
<td>17</td>
<td>34</td>
<td>Skeletal dysplasia</td>
<td>Yes (69%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>33</td>
<td>CCAM</td>
<td>Yes (52%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>33</td>
<td>CDH</td>
<td>Yes (52%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>35</td>
<td>CCAM</td>
<td>Yes (64%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>36</td>
<td>CDH</td>
<td>Yes (55%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>31</td>
<td>Small chest</td>
<td>Yes (54%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>31</td>
<td>CDH</td>
<td>Yes (35%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>CDH</td>
<td>Yes (61%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>31</td>
<td>Twin-twin transfusion syndrome</td>
<td>Yes (35%)</td>
<td>Lethal pulmonary hypoplasia</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>34</td>
<td>CCAM</td>
<td>Yes (35%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>36</td>
<td>CDH</td>
<td>Yes (50%)</td>
<td>Live born</td>
<td></td>
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<tr>
<td>28</td>
<td>32</td>
<td>Oligohydramnios</td>
<td>Yes (50%)</td>
<td>Live born</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>31</td>
<td>CCAM</td>
<td>Yes (34%)</td>
<td>Live born</td>
<td></td>
</tr>
</tbody>
</table>

Non-reactive

Reactive

Sensitivity: 92%
Specificity: 82%
PPV: 79%
NPV 93%

2002 R. Broth et al.
MRI (LLSIR) at 29 weeks

Rt

Lung
Liver

Lt

Lung
Heart

Coronal

LLSIR=