Congenital Diaphragmatic Hernia
Update on fetal diagnosis

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FIMATHO
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Inserm

European Reference Network
for rare or low prevalence complex diseases
Network Inherited and Congenital Anomalies (ERNICA)

Plateforme d'Expertise Paris-Sud MALADIES RARES

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

Prevalence and diagnosis

- Epidemiology of CDH using data from high quality, population based registers belonging to EUROCAT
- CDH cases, 1980-2009, 31 registers, 12M births
- 10.4% associated with chromosomal anomalies or genetic syndrome
- 28.2% with major structural anomalies
- Male/female: 1:0.69
- Prevalence
  - 2.3 (95%CI 2.2 to 2.4) per 10 000 births
  - 1.6 (95%CI 1.6 to 1.7) per 10 000 births when isolated

Canada: 3.38/10 000 *(ICBDSR Annu Rep 2014)*

USA: 1.93/10000 (Balayla J et al, J Maternal Fetal Med, 2014)

Utah: 3.17/10 000 *(Shanmugam H et al, Birth Defect Research, 2017)*

McGivern MR et al. Arch Dis Child Fetal Neonatal Ed, 2015

Prevalence and diagnosis

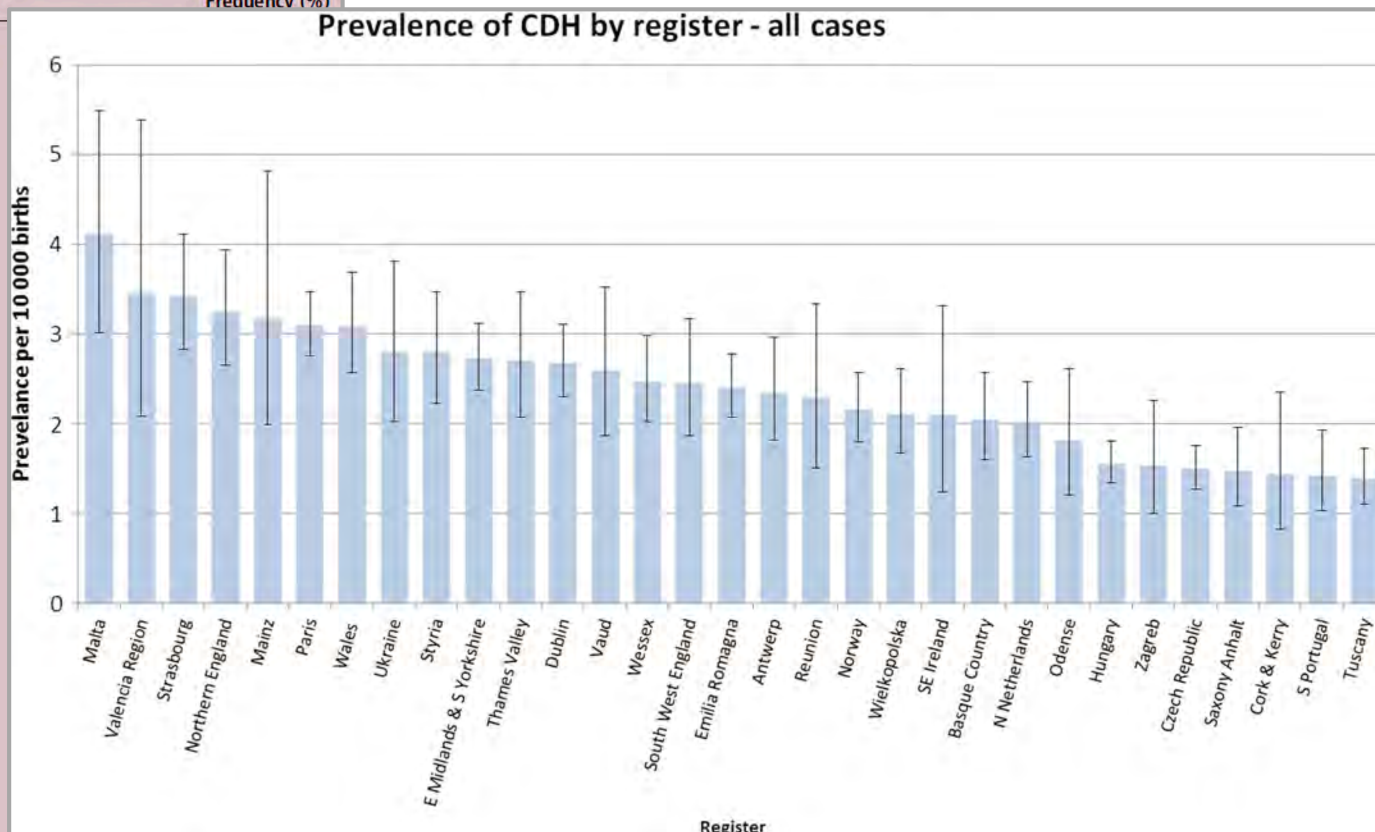
- Increase prevalence over time but not for isolated cases
- Variations among countries
- Mean gestational age at delivery: 39 weeks (IGR 37-40)
- Outcomes overall/isolated
  - Live birth 83.4% /88.7%
  - TOP 13% (4.6% in 1980-84 to 14.4% 2005-09)/8.9% (1.6% to 10.4%)
  - Stillbirth 3.6%/2.4%
- No effect of maternal age

McGivern MR et al. Arch Dis Child Fetal Neonatal Ed, 2015

Prevalence and diagnosis

Table 1 Commonly associated structural anomalies in singleton cases of congenital diaphragmatic hernia (n=2776)

Most common associated anomalies	Frequency (%)
Cardiac anomalies	
Ventricular septal defect	
Atrial septal defect	
Hypoplastic left heart	
Coarctation of aorta	
Urinary	
Congenital hydronephrosis	
Limb	
Limb reduction	
Upper limb reduction	
Lower limb reduction	
Club foot—talipes equinovarus	
Polydactyly	
Syndactyly	
Respiratory (specific groups)	
Nervous system	
Neural tube defects	
Hydrocephalus	
Spina bifida	
Anencephalus and similar	
Oro-facial clefts	
Cleft lip with or without palate	
Cleft palate	
Digestive system (excluding CDH)	
Ano-rectal atresia	
Abdominal wall defects	
Genital	51 (1.8)
Hypospadias	21 (0.8)
Ear, face and neck	43 (1.5)
Eye	18 (0.6)

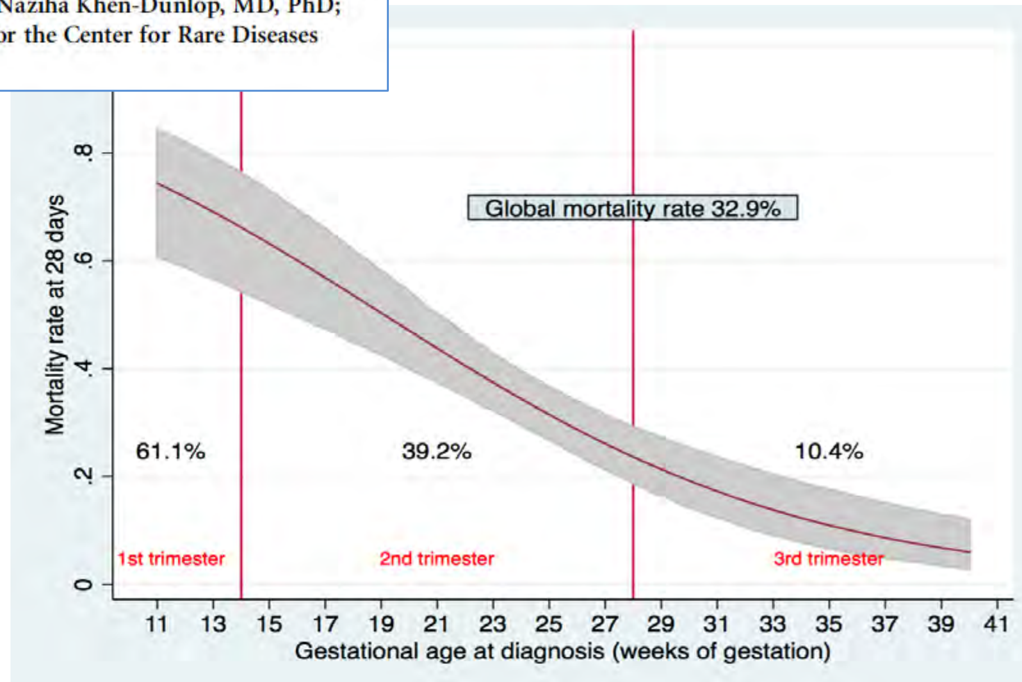


McGivern MR et al. Arch Dis Child Fetal Neonatal Ed, 2015

Congenital diaphragmatic hernia: does gestational age at diagnosis matter when evaluating morbidity and mortality?

Hanane Bouchghoul, MD; Marie-Victoire Senat, MD, PhD; Laurent Storme, MD, PhD; Pascal de Lagausie, MD, PhD; Laetitia Begue, MD; Naziha Khen-Dunlop, MD, PhD; Jean Bouyer, PhD; Alexandra Benachi, MD, PhD; for the Center for Rare Diseases for Congenital Diaphragmatic Hernia

2009-2013: 5% of cases diagnosed at first trimester
Sample size n=377



Mortality rate at 48h and 28 d decreases with GA at diagnosis (p<0.001) (adjustment for size of the hernia, thoracic herniation of the liver, GA at birth, LHRo/e, FETO)

Bouchghoul H et al. Am J Obstet Gynecol, 2015

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

Hernie de coupole diaphragmatique

Hernie de coupole diaphragmatique
Centre de Maladie Rare

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Centre de Référence des Hernies Diaphragmatiques

Centre des Mardi.org
Le portail des maladies rares digestives

Cracmo
Centre de référence des affections congénitales et malformatives de l'œsophage

PaRaDis
Pancreatic Rare Diseases
Centre de référence des maladies rares

European Reference Network
for rare or low prevalence complex diseases

Network
Inherited and Congenital Anomalies (ERNICA)

CDH – Prognostic Evaluation

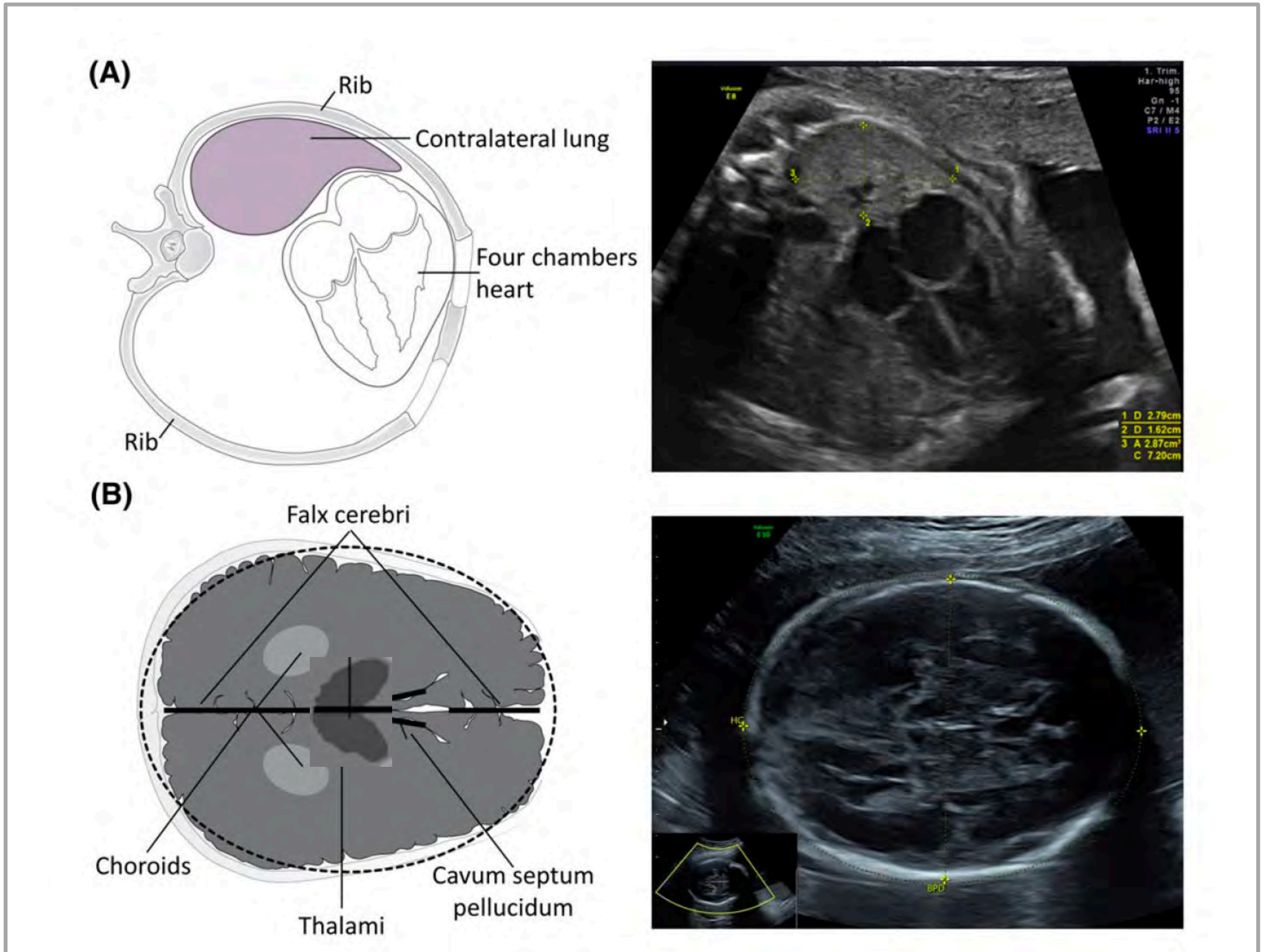
Proposal for standardized prenatal ultrasound assessment of the fetus with congenital diaphragmatic hernia by the European reference network on rare inherited and congenital anomalies (ERNICA)

Francesca Maria Russo[1,2] | Anne-Gael Cordier[3] | Luc De Catte[1,2] | Julien Saada[4] | Alexandra Benachi[3,4] | Jan Deprest[1,2,5] |
on behalf of the Workstream Prenatal Management, ERNICA European reference network

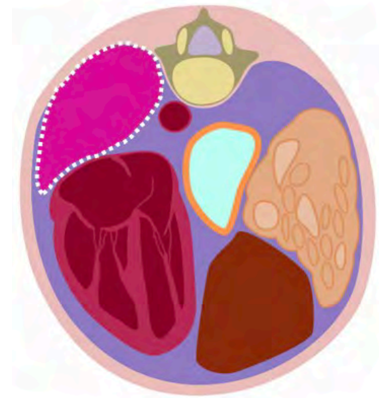
We provide a practical and instructional guide for the standardized assessment of fetuses with isolated left or right congenital diaphragmatic hernia and individualized prediction of neonatal outcome.

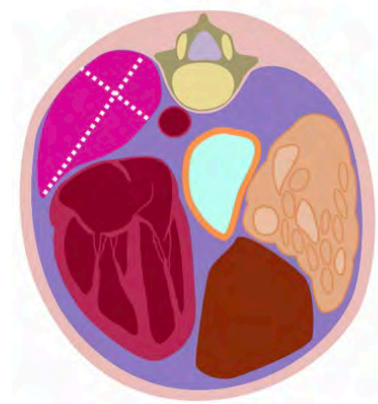
Russo FM et al. Prenat Diagn, 2018

Prognostic Evaluation-LHR o/e



Trace method

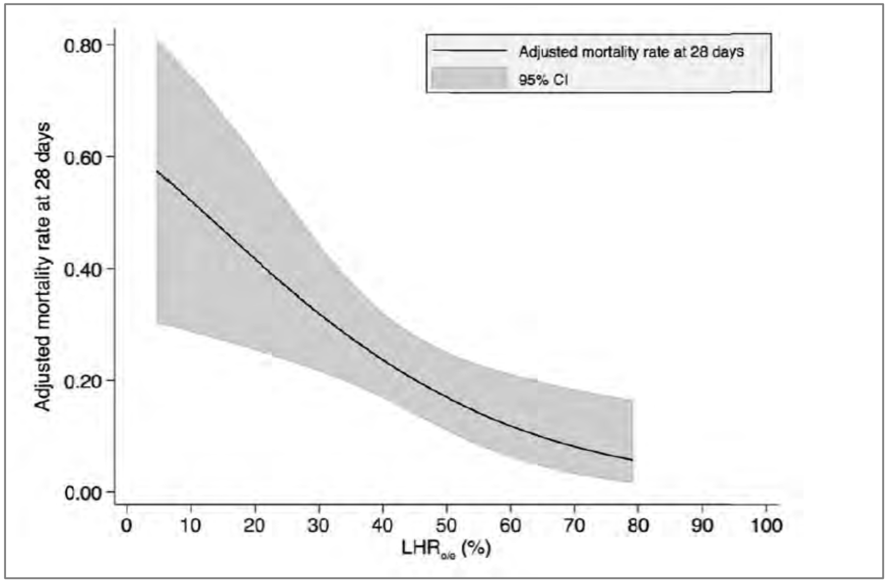




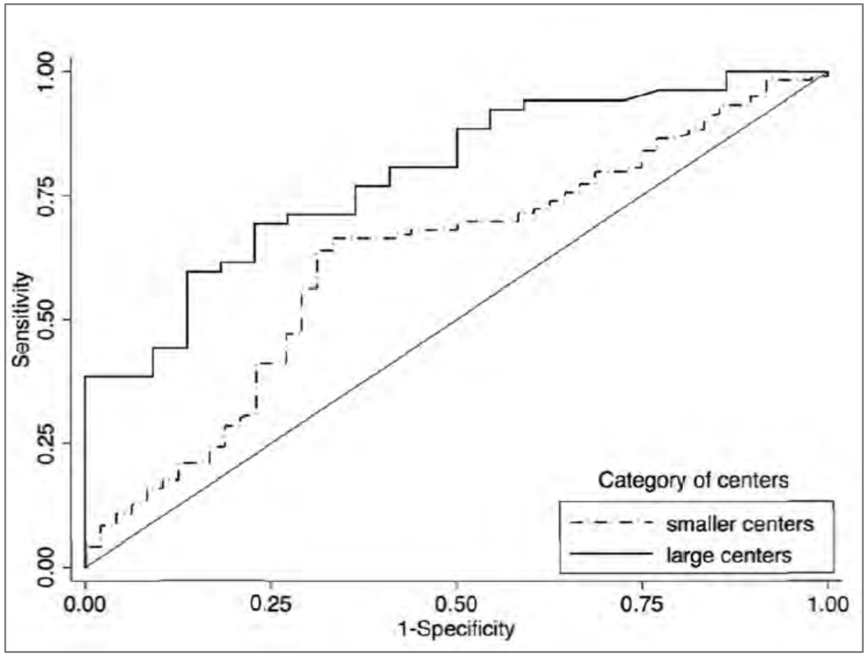
Longest diameters method

Jani J et al, Ultrasound Obstet Gynecol 2012
Russo FM et al, Prenat Diagnosis, 2018

Prognosis of isolated congenital diaphragmatic hernia using lung-to-head circumference ratio: variability across centers in a national perinatal network



Adjusted relationship between 28-days mortality and o/e LHR



Predictive capacity (AUC) of o/e-LHR for 28 days survival according to category of centers (< ou ≥ 14/year)

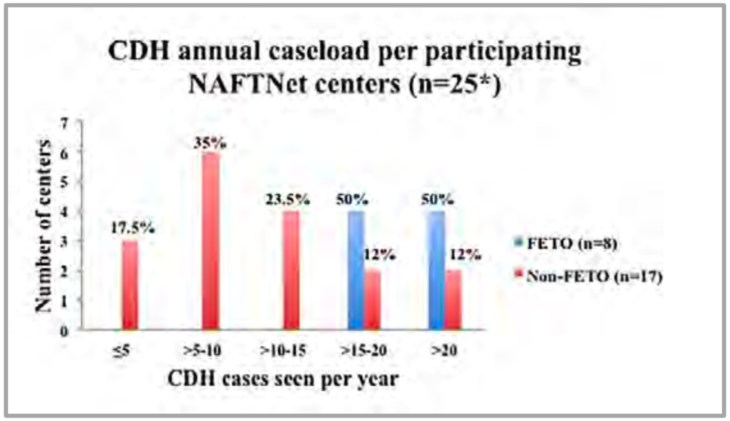
The overall predictive value of o/e-LHR is better when prenatal LHR measurements are performed in centers with the greatest caseload and strong expertise in prenatal assessment of CDH

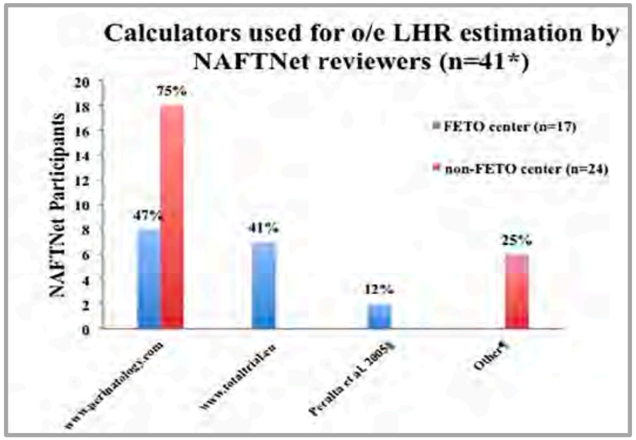
Senat et al. Ultrasound Obstet Gynecol, 2017

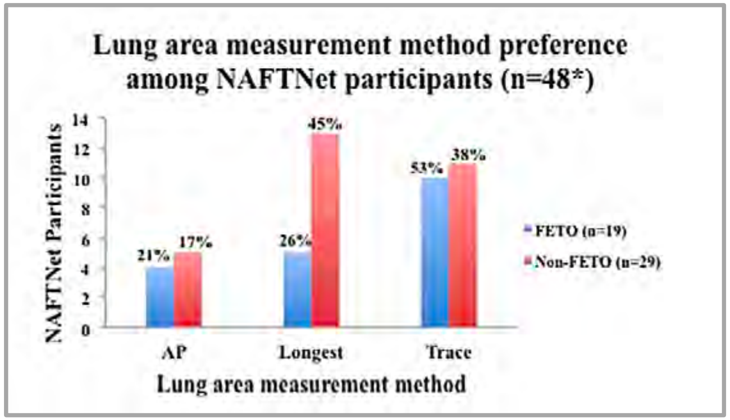
Hôpitaux universitaires Paris-Sud

Prognostic Evaluation-LHR o/e

Variability in antenatal prognostication of fetal diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)







- Image selection for measurements: Landmarks of a true axial plane and 4-chamber view of the heart
- Formula: *Jani et al. USOG 2012*

Abbasi N et al. Prenat Diagnosis, 2019

Prognostic Evaluation-LHR o/e

Reproducibility of fetal lung-to-head ratio in left diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)

- Comparison of lung area measurement methods on de-identified sonographic clips of left CDH across 26 centers (17 non-FETO and 9 FETO) within the North American Fetal Therapy Network and in comparison with an external European reviewer
- The trace method demonstrated the highest inter-rater agreement with the lowest bias
- Lower expertise in non FETO centers, lower agreement in HC measurements also
- Only for left CDH

Abbasi N et al. Prenat Diagnosis, 2019

Prognostic Evaluation-LHR o/e

The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study

Kitty G. Snoek[1†], Nina C. J. Peters[2*†], Joost van Rosmalen[3], Arno F. J. van Heijst[4], Alex J. Eggink[2], Esther Sikkel[5], René M. Wijnen[1], Hanneke IJsselstijn[1], Titia E. Cohen-Overbeek[2] and Dick Tibboel[1]

- Evaluate predictive value of o/e LHR for survival and chronic lung disease in an era of standardized neonatal management
  - Retrospective cohort, 2 high volume centers in Netherlands
  - 122 isolated cases 2008-2014
- 77.9% survived and 38.9% CLD
  - First measured o/e LHR significantly predict survival and CLD

Snoek KG et al. Prenat Diagn, 2017

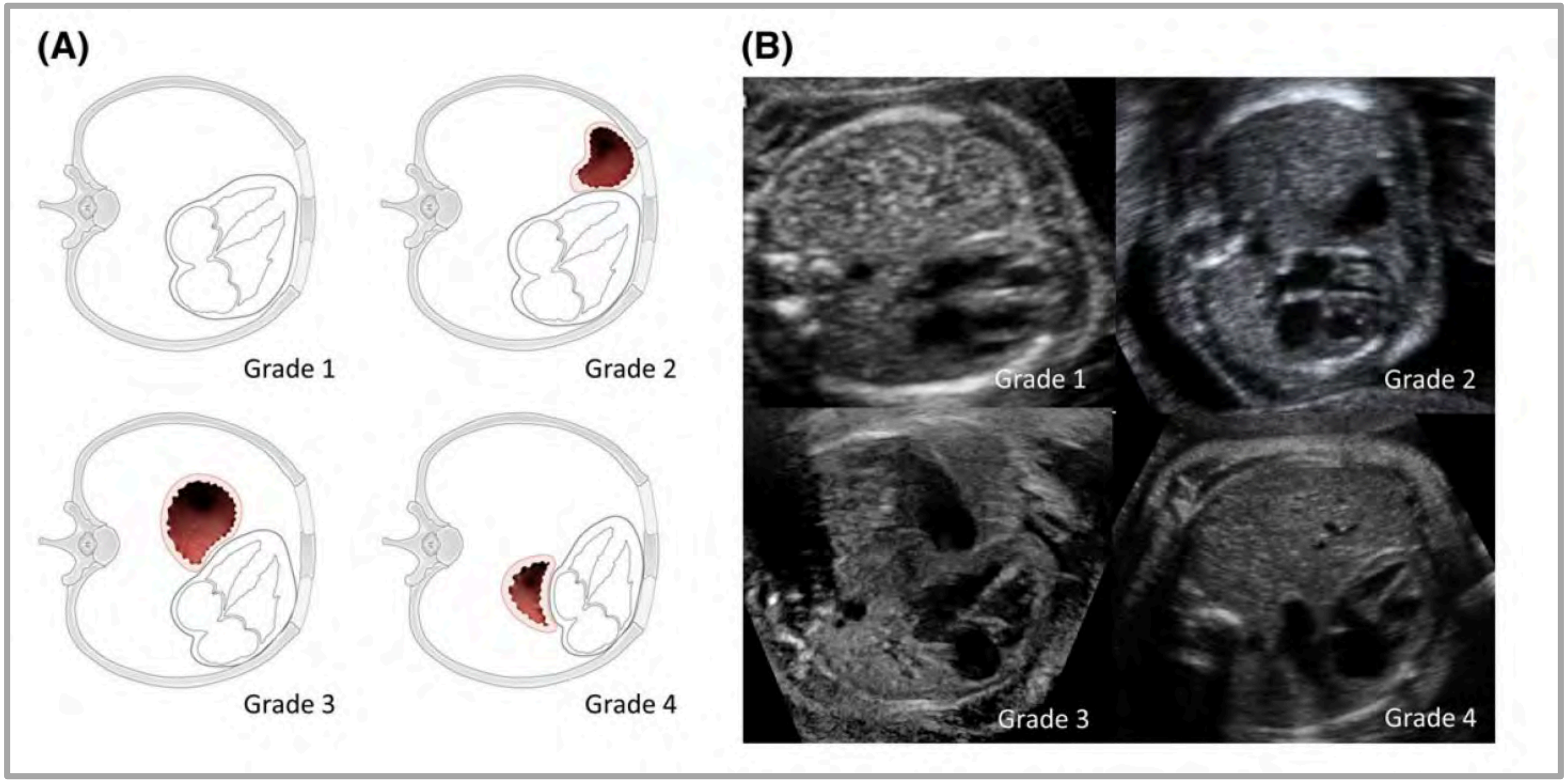
Prognostic Evaluation-LHR o/e

Clinically relevant discordances identified after tertiary reassessment of fetuses with isolated congenital diaphragmatic hernia

	Assessment referrals	Fetal surgery referrals	Entire population over 2-year period	
N (%)	43 (33%)	86 (67%)	129	*P*-value
Descriptive statistics (based on assessment at FETO-unit)				
No CDH		2		
Right CDH	5/43 (12%)	13/84 (15%)	18/127 (14%)	ns
Liver up	5/5 (100%)	12/13 (92%)	17/18 (94%)	ns
O/E LHR	32.13%	25.8%	31.4%	ns
Left CDH	38/43 (88%)	71/84 (85%)	109/127 (86%)	ns
Liver up	29/38 (76%)	59/71 (83%)	88/109 (81%)	ns
O/E-LHR	30.9%	23%	24%	ns
% with severe lung hypoplasia[a]	13/38 (34%)	43/71 (61%)	56/109 (51%)	<0.005
Discordance between referring center and FETO-unit				
Absence of DH	0	2/86 (2%)	2 (2%)	
Presence of associated anomalies	6/43 (14%)	8/86 (10%)	14/129 (11%)	ns
Liver discordance	9/18 (50%)	2/29 (7%)	11/47 (23%)	<0.005
Overestimated severity	1/18 (5%)	1/29(3%)	2/47 (4%)	ns
Underestimated severity	8/18 (44%)	1/29(3%)	9/47 (19%)	<0.005
O/E LHR	3/8 (38%)	8/24 (33%)	11/32 (34%)	ns
Overestimated lung size >10%	0/8 (0%)	0/8 (0%)	0/16 (0%)	ns
Underestimated lung size >10%	3/8 (38%)	8/24 (33%)	11/32 (34%)	ns

Done E et al. Prenat Diagn, 2017

Prognostic Evaluation-Liver position



Cordier AG et al. Ultrasound Obstet Gynecol, 2015
Russo FM et al. Prenat Diagn, 2018

Prognostic Evaluation-Liver position

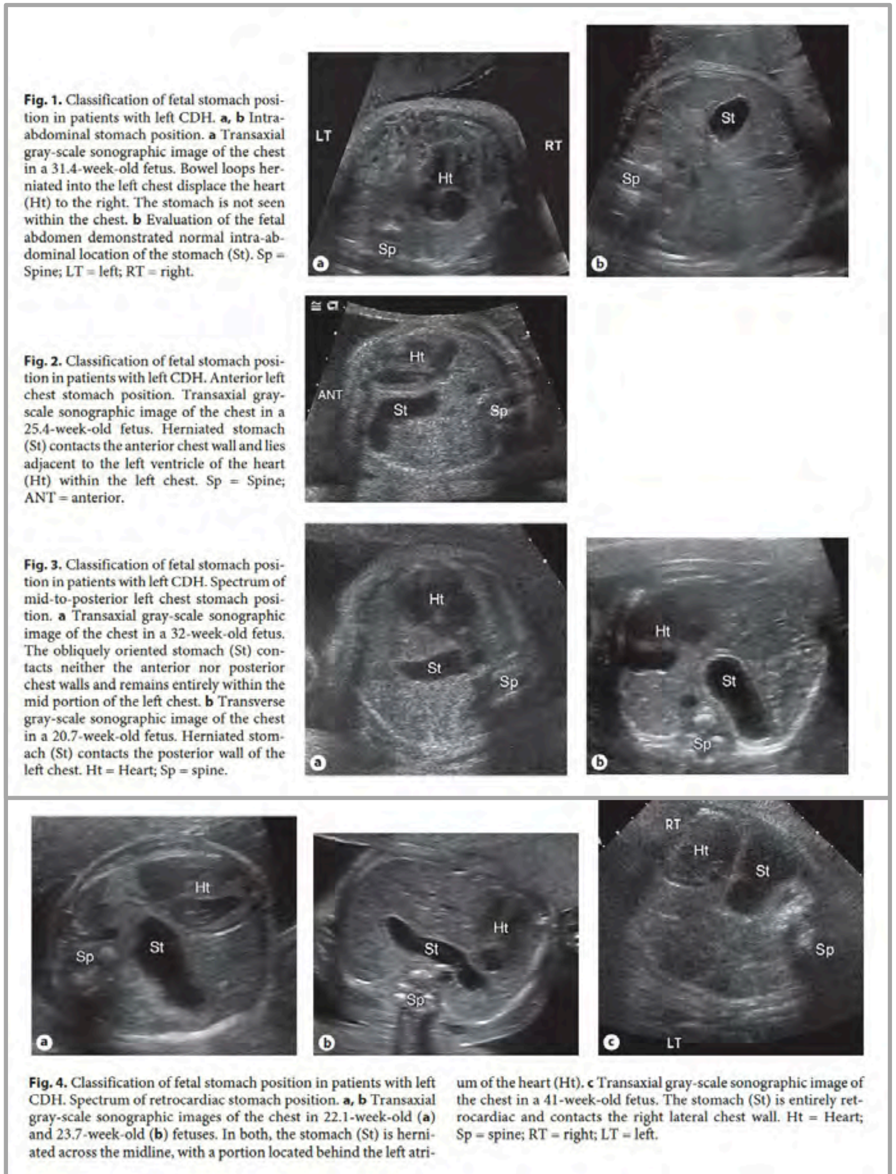


Fig. 1. Classification of fetal stomach position in patients with left CDH. **a, b** Intra-abdominal stomach position. **a** Transaxial gray-scale sonographic image of the chest in a 31.4-week-old fetus. Bowel loops herniated into the left chest displace the heart (Ht) to the right. The stomach is not seen within the chest. **b** Evaluation of the fetal abdomen demonstrated normal intra-abdominal location of the stomach (St). Sp = Spine; LT = left; RT = right.

Fig. 2. Classification of fetal stomach position in patients with left CDH. Anterior left chest stomach position. Transaxial gray-scale sonographic image of the chest in a 25.4-week-old fetus. Herniated stomach (St) contacts the anterior chest wall and lies adjacent to the left ventricle of the heart (Ht) within the left chest. Sp = Spine; ANT = anterior.

Fig. 3. Classification of fetal stomach position in patients with left CDH. Spectrum of mid-to-posterior left chest stomach position. **a** Transaxial gray-scale sonographic image of the chest in a 32-week-old fetus. The obliquely oriented stomach (St) contacts neither the anterior nor posterior chest walls and remains entirely within the mid portion of the left chest. **b** Transverse gray-scale sonographic image of the chest in a 20.7-week-old fetus. Herniated stomach (St) contacts the posterior wall of the left chest. Ht = Heart; Sp = spine.

Fig. 4. Classification of fetal stomach position in patients with left CDH. Spectrum of retrocardiac stomach position. **a, b** Transaxial gray-scale sonographic images of the chest in 22.1-week-old (**a**) and 23.7-week-old (**b**) fetuses. In both, the stomach (St) is herniated across the midline, with a portion located behind the left atrium of the heart (Ht). **c** Transaxial gray-scale sonographic image of the chest in a 41-week-old fetus. The stomach (St) is entirely retrocardiac and contacts the right lateral chest wall. Ht = Heart; Sp = spine; RT = right; LT = left.

- Prognostic factor by itself and not a proxy of liver herniation
- No precise landmarks

Basta AM et al. Fetal Diagn Ther, 2016

Correlation between stomach grading and Gastrointestinal morbidity

- Correlation between defect size and global morbidity

  3665 patients. Overall survival 70.9%

  – 61.7% gastrointestinal morbidity

  – Median age at discharge 38 d :

    - 22 d group A à 89 d group D

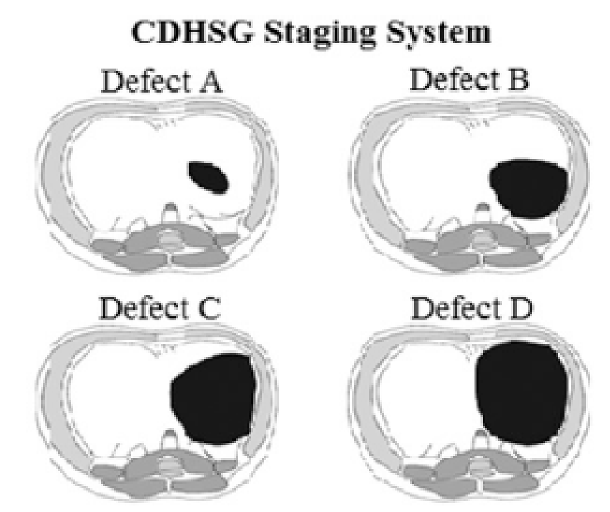


TABLE 3 Morbidity Outcomes at Discharge Based on CDH Defect Size

	All Patients (N = 2183)	No. Missing Data	Defect A (n = 370)	Defect B (n = 979)	Defect C (n = 644)	Defect D (n = 177)	P[a]
Any morbidity	1503 (74.6)	167	209 (61.8)	612 (68.4)	514 (85.4)	159 (94.1)	<.001
Pulmonary morbidity	661 (30.4)	6	44 (12.0)	181 (18.5)	312 (48.5)	120 (68.2)	<.001
Supplemental oxygen	417 (19.2)	7	20 (5.5)	95 (9.7)	204 (31.8)	94 (53.4)	<.001
Pulmonary medication	524 (24.0)	0	30 (8.1)	133 (13.6)	246 (38.2)	111 (62.7)	<.001
Neurologic morbidity	447 (21.7)	125	40 (11.7)	137 (15.0)	183 (29.8)	79 (45.7)	<.001
Abnormal neurologic examination	437 (21.2)	125	40 (11.7)	134 (14 6)	177 (28.8)	78 (45.1)	<.001
Neurologic medication	40 (1.8)	0	3 (0.8)	8 (0.8)	18 (2.8)	10 (3.6)	<.001
Gastrointestinal morbidity	1349 (65.2)	114	183 (51.7)	543 (58.8)	474 (77.7)	144 (85.2)	<.001
Supplemental tube feeds	660 (30.5)	22	45 (12.2)	183 (18.9)	309 (48.6)	119 (68.8)	<.001
Gastroesophageal reflux	1227 (58.8)	97	162 (45.6)	496 (53.3)	437 (70.9)	128 (74.4)	<.001
Diagnosed clinically	903 (76.9)	52	144 (90.6)	393 (83.3)	298 (72.7)	62 (50.0)	<.001
Diagnosed radiologically	272 (23.1)		15 (9.4)	80 (16.7)	112 (27.3)	62 (50.0)	<.001
Nuclear scan	33 (12.1)		3 (20.0)	8 (10.0)	12 (10.7)	9 (14.5)	
Upper gastrointestinal series	219 (80.5)	0	10 (66.7)	69 (36.3)	90 (80.4)	48 (77.4)	.564
pH probe	20 (7.4)		2 (13.3)	3 (3.7)	10 (8.9)	5 (8.1)	
Medical therapy	1008 (84.4)		154 (96.3)	450 (92.4)	328 (78.3)	74 (58.7)	
Surgical therapy	184 (15.4)	32	5 (3.1)	35 (7.2)	91 (21.7)	51 (40.5)	<.001
No therapy given	3 (0.2)		1 (0.6)	1 (0.2)	0 (0)	1 (0.8)	
Gastrointestinal medication	353 (16.2)	0	54 (14.6)	145 (14.8)	110 (17.1)	43 (24.3)	.012
Median time on ventilator, d	13 (7–24)	37	7 (4–10)	10 (7–16)	22 (14–34)	30 (22–50)	<.001
Median hospital length of stay, d	38 (23–69)	4	22 (16–32)	31 (22–47)	62 (39–96)	89 (64–132)	<.001

Data are presented as n (%) or median (IQR).

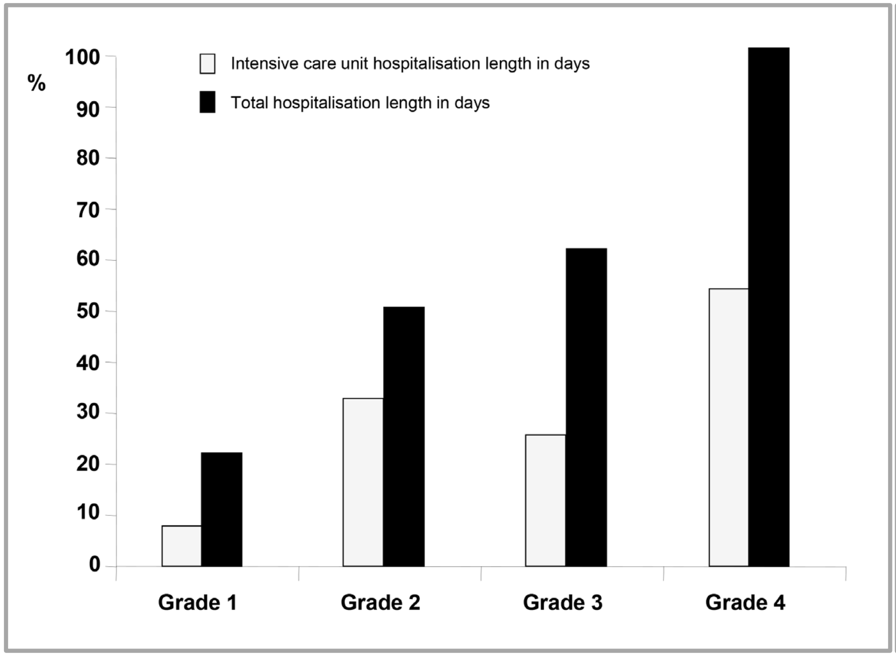
[a] χ^2 or Kruskal–Wallis rank tests comparing these patients with patients without morbidities.

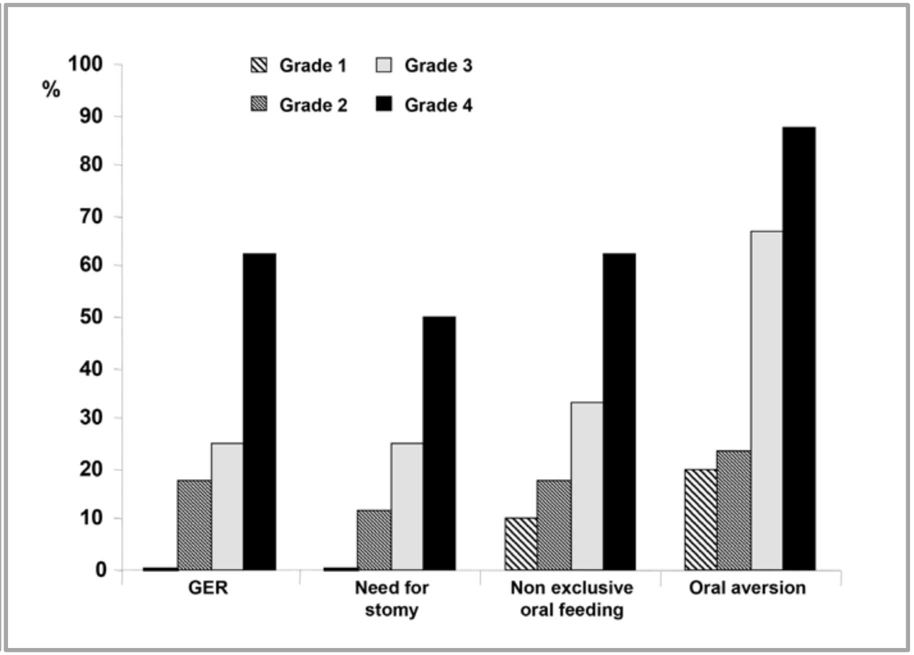
Putnam LR et al. Pediatrics. 2016

Correlation between stomach grading and Gastrointestinal morbidity

Stomach grade (1 à 4)

47 children at 2 years



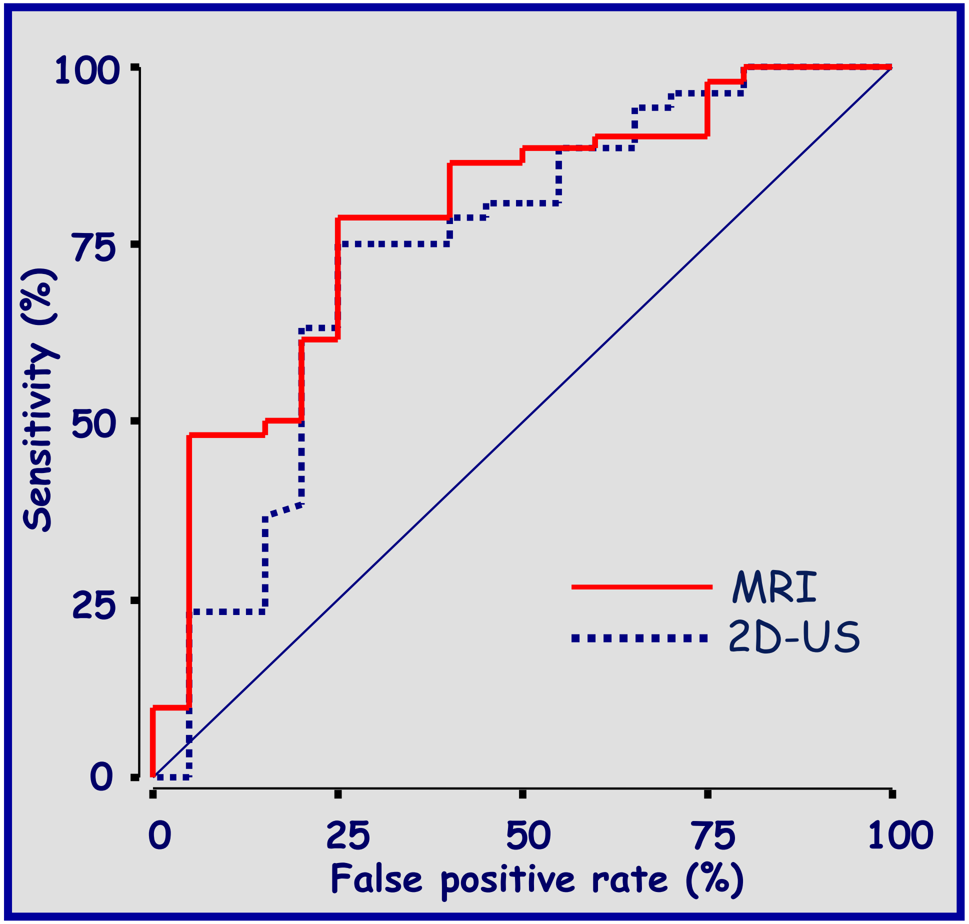


…… Seems to be Independent of FETO

- Same findings at 6 months *Verla MA et a. Fetal Diagn 2019*
- Need for homogenized assessment and follow up of oral disorder and GER

Cordier AG et al, submitted

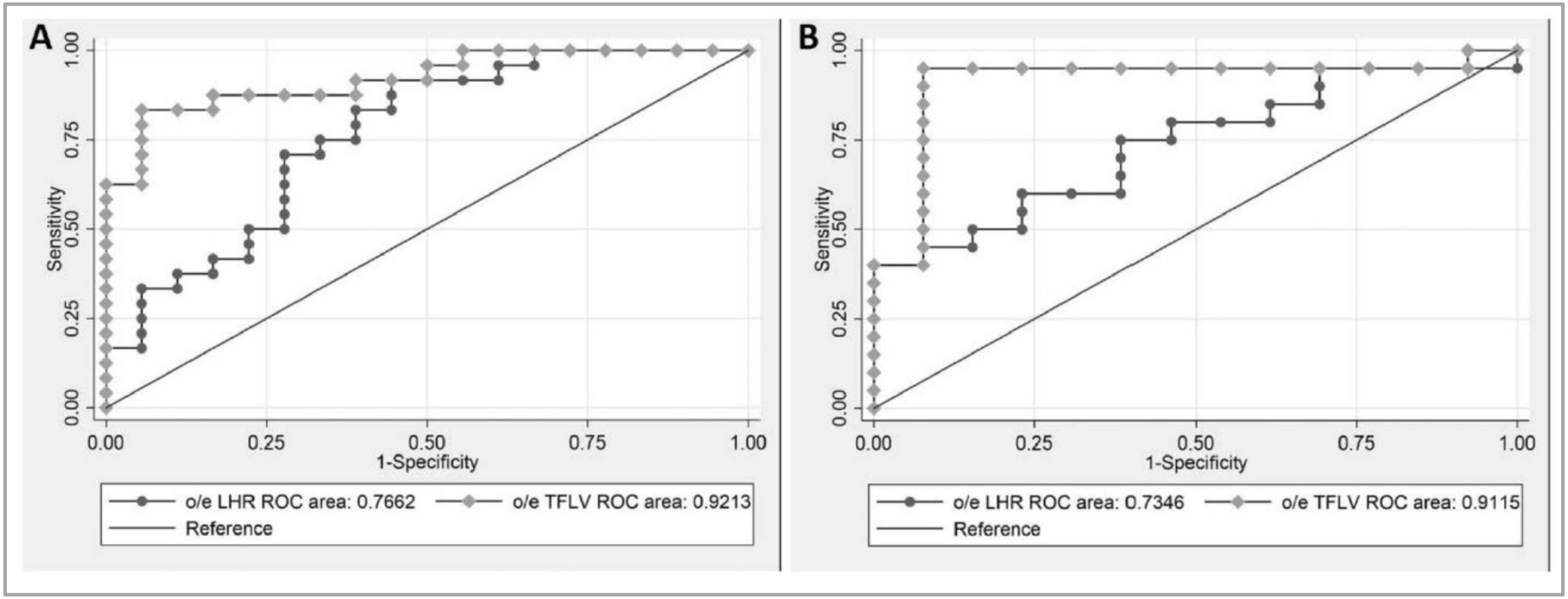
o/e LHR (2D-US) vs o/e Total lung (MRI)



MRI better than 2D LHR in prediction of survival

Jani J et al. Ultrasound Obstet Gynecol, 2008

o/e LHR (2D-US) vs o/e Total lung (MRI)



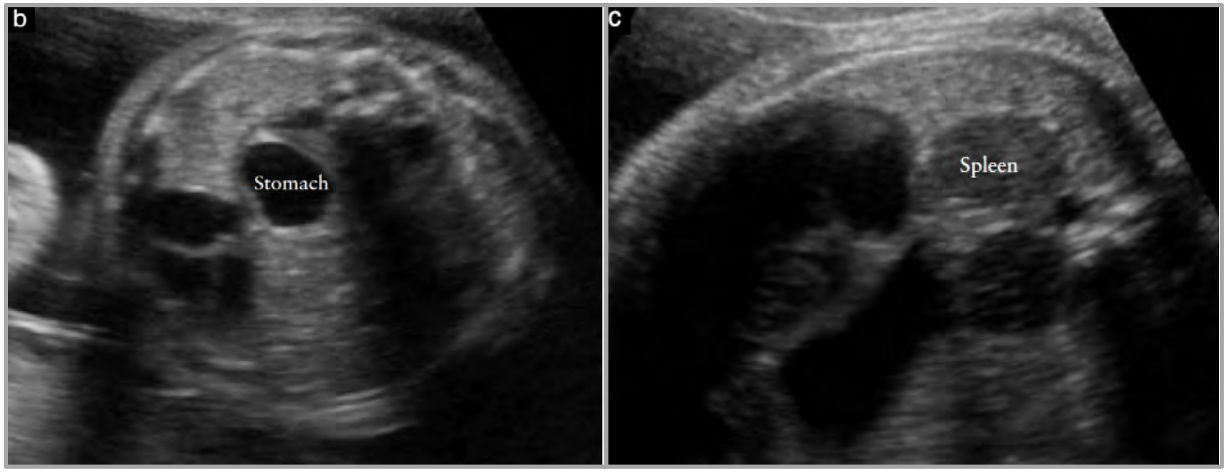
MRI better than 2D LHR in prediction of

- Survival
- Defect size

Kim AG et al. J Ped Surg, 2019

o/e LHR (2D-US) vs o/e Total lung (MRI)

- Reasons for MRI superiority
  - Lung measurement by MRI easier to standardized
  - Both lungs are evaluated
- Reasons for discordance
  - Patient characteristics
  - Fetal position
  - Different timing at measurement and presence of a large stomach or spleen

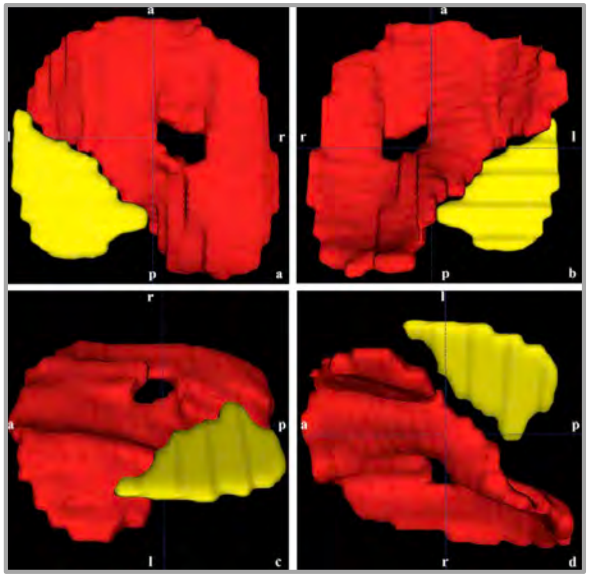


Jani J et al. Ultrasound Obstet Gynecol, 2012

Three-dimensional reconstruction of defects in congenital diaphragmatic hernia: a fetal MRI study

F. PRAYER[1], M. METZELDER[2], W. KROIS[2], P. C. BRUGGER[3], G. M. GRUBER[3], M. WEBER[1], A. SCHARRER[4], A. ROKITANSKY[5], G. LANGS[6], D. PRAYER[1], E. UNGER[7] and G. KASPRIAN[1]

- To assess the clinical feasibility and validity of fetal MRI-based 3D reconstructions to localize, classify, and quantify diaphragmatic defects in congenital diaphragmatic hernia
- Areas of the intact diaphragm and the defect were measured and defect-to-diaphragmatic ratios (DDR) were calculated
- The need for prosthetic patch repair and diaphragm growth dynamics, in cases with repeated in vivo fetal MRI scans, were analyzed based on DDR.



Prayer F et al. Ultrasound Obstet Gynecol, 2019

Prognostic evaluation - R CDH

o/e LHR o/e - Survival

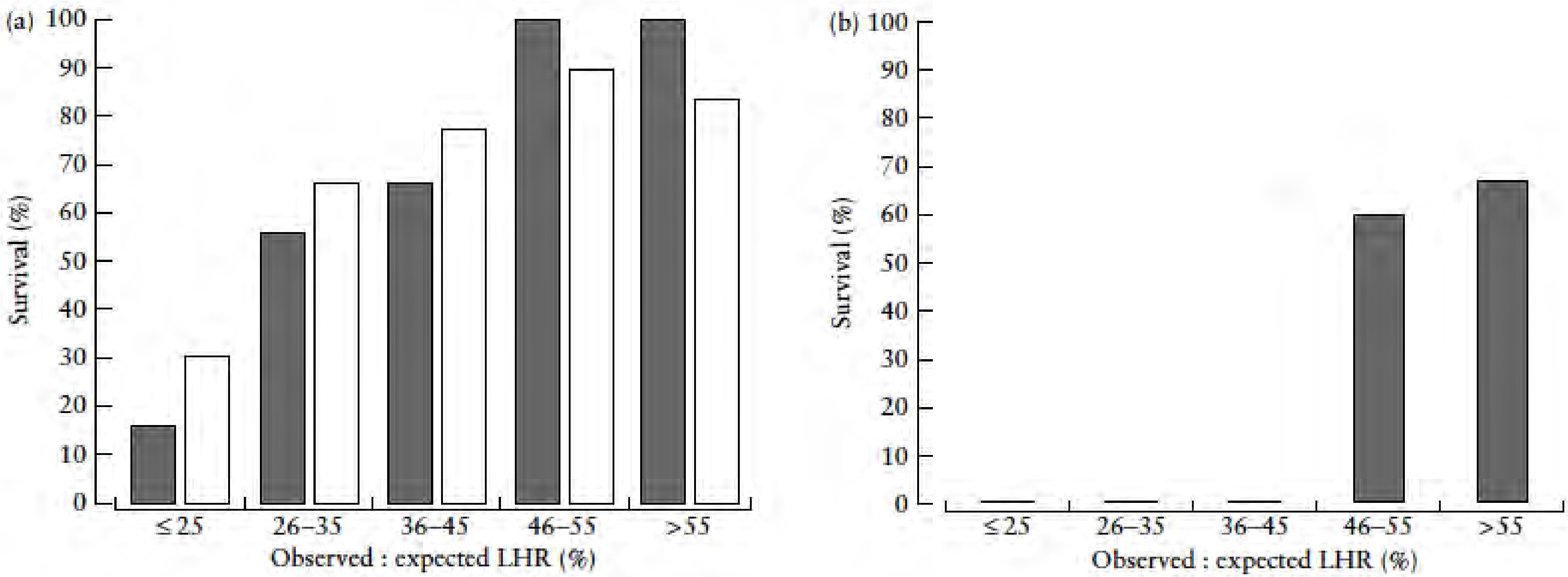


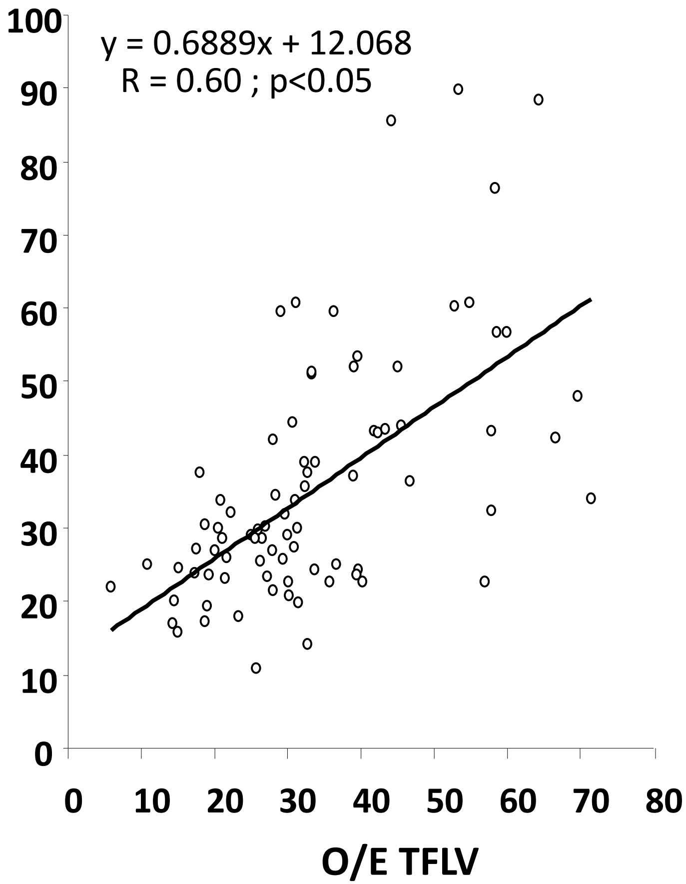
Figure 3 Survival rate according to the fetal observed to expected lung area to head circumference ratio (LHR) in fetuses with isolated left-sided (a) and right-sided (b) diaphragmatic hernia. The filled bars represent fetuses with intrathoracic herniation of the liver and the open bars represent those without herniation.

Jani J et al. Ultrasound Obstet Gynecol, 2007

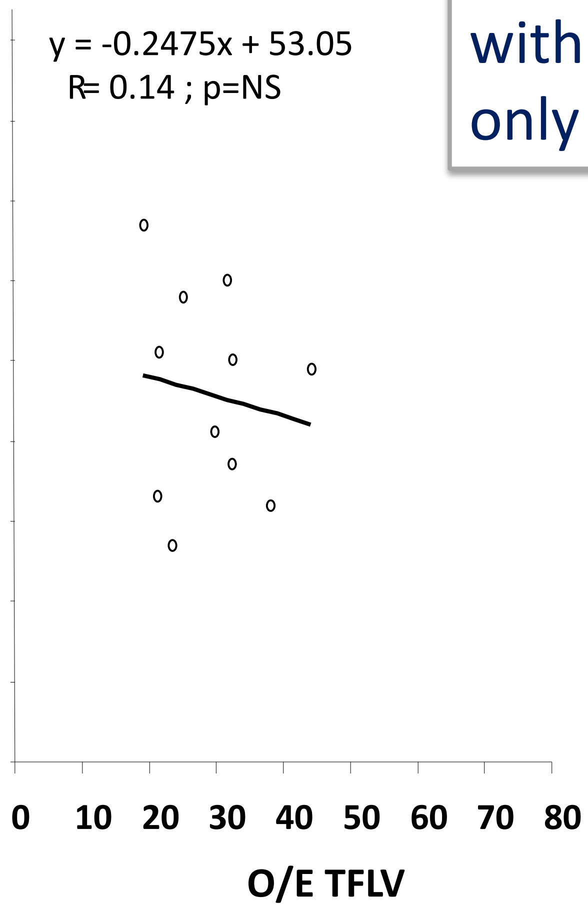
Prognostic evaluation - R CDH

o/e LHR vs o/e TFLV

N= 82 L-CDH



N = 11 R-CDH



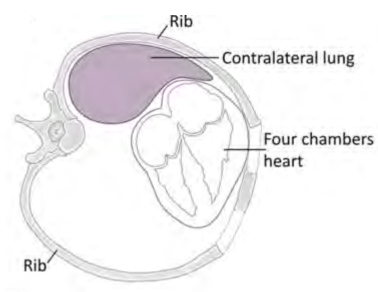
o/e LHR correlates with o/e TFLV at MRI only for left CDH

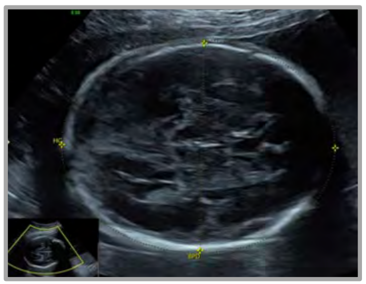
Prognostic evaluation - R CDH

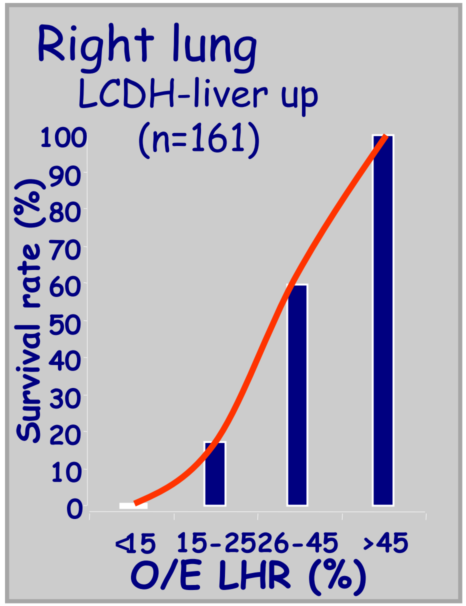
- Controversy over the prognosis due to lack of power and control group in some series
- Identical means of pulmonary volumes for L and R CDH
- Liver amount intra-thoracic is higher in R CDH
- No correlation in R CDH between o/e LHR and
  - Lung volume at pathological examination
  - Lung volume at MRI
  - Therefore, not a good reflection of the total lung volume
- No information on outcome in those studies

- L and R CDH should not be pooled together in series

Prognostic Evaluation- CDH





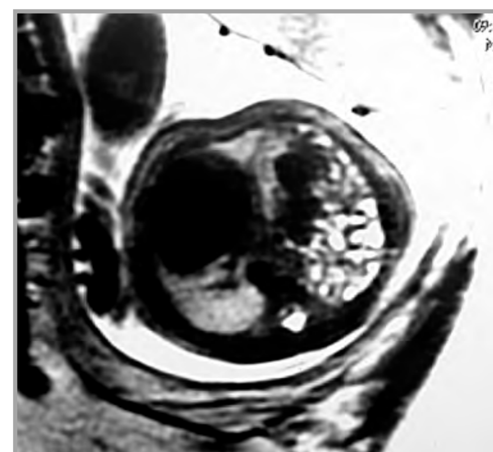


- Detailed scan
- Vascularization
- Heart
- Sac evaluation
- Genetics

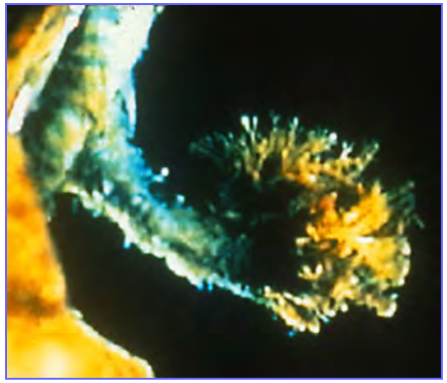
o/e LHR

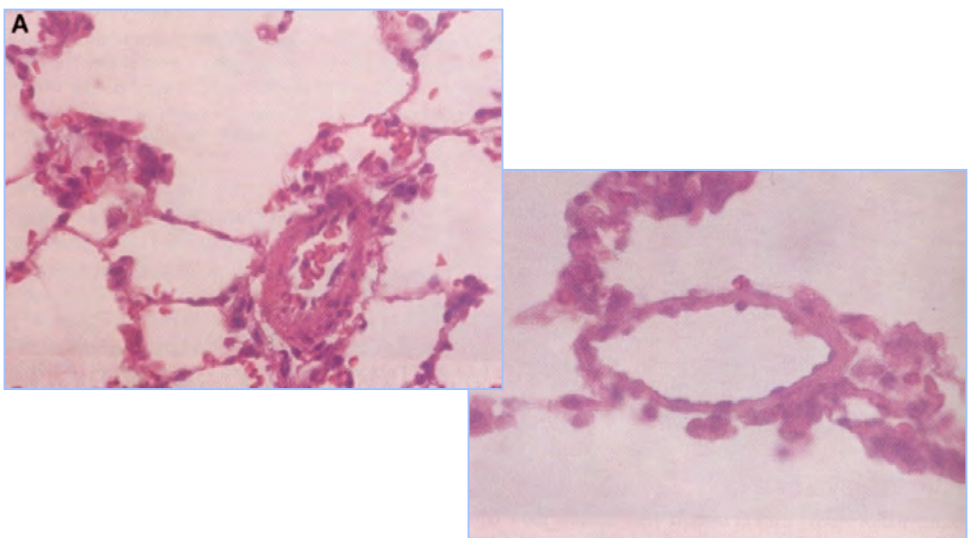
o/e TLV MRI

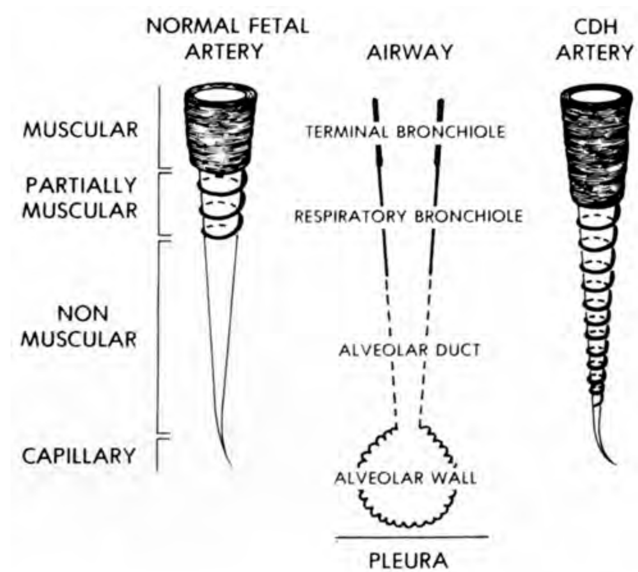
Liver position



Pulmonary volume does not always correlate with function



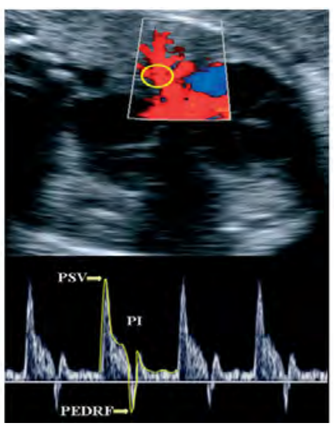




CDH and vascularisation

Aims

- Evaluation of pulmonary hypoplasia
- In addition to the o/e LHR
- Prediction of Pulmonary Hypertension



Techniques

- Pulmonary artery Doppler
  - PI, RI, PSV,PEDRF…
  - Acceleration Time, Ejection Time
- Pulmonary vascularisation index
- Arteries diameter
- Energy Doppler
- 3D Energy Doppler
- Hyperoxygenation

Moreno-Alvarez O et al., 2008
Ruano R et al., 2006

Pulmonary vascularisation Index

- Many papers, lots of measurements and…. not so many conclusive results
- Measurements are sonographer dependent
- Improvement of post-natal care makes prediction of mortality difficult *(Sokol J, 2008)*
- Pulmonary Hypertension linked to intra-parenchymal vascular anomalies
- Functional test

Prenatal heart

- "There is increasing evidence that cardiac dysfunction is a key contributor to CDH pathophysiology".
- Left Ventricular dysfunction= association of pathological factors in the transition period
  - Reduced pulmonary blood flow and LV preload
  - LV hypoplasia
  - Acute increase in LV afterload at birth
  - Negative effects of systemic hypoxia and acidosis

Patel N et al. Seminars in Perinatol,2019

Prenatal heart

Table 1 – Echocardiographic techniques for assessment of pulmonary artery pressure and cardiac function in congenital diaphragmatic hernia.		
Parameter	Technique	Notes and limitations
Pulmonary artery pressure assessment		
Peak Tricuspid Regurgitation Velocity (TR_{max})	Estimates RV peak systolic pressure using modified Bernoulli equation ($RVSP = 4(TR_{max})^2$)	TR_{max} may be absent or difficult to measure accurately.
Patent arterial duct (PDA) flow	Doppler assessment of direction & velocity, estimates PAP relative to systemic BP	Requires patent ductus. Qualitative assessment of PAP.
Interventricular shape and position	Indirect assessment of right ventricular pressure and PAP	Qualitative assessment only.
Acceleration time: right ventricular ejection time ratio (AT:RVET)	Time intervals measured from Doppler of RV outflow.	Correlates with pulmonary vascular resistance. Does not quantify PAP.
Cardiac function assessment		
"Eyeball" of function from 2D loop	Subjective assessment of function from 2D images in long and short axes	Subjective, qualitative, high inter-observer variability
Ejection Fraction (EF)	Percentage of change in LV volume from end- diastole to end-systole	Angle- and load-dependent, inter-observer variability, affected by septal shape and dysfunction.
RV Fractional Area Change (FAC)	Percentage change in RV area between end-diastole and end-systole	Load dependent, high inter-observer variability. Global measure of function.
Tricuspid Annular Systolic Excursion (TAPSE)	Longitudinal displacement of the lateral tricuspid valve annulus during systole	Highly load- and angle-dependence. Assesses systolic function only.
Atrio-ventricular valve (AV) inflow	Doppler analysis of diastolic inflow to ventricles	Diastole only, highly load-dependent.
Right and Left Ventricular Outflow (RVO and LVO)	Estimation of ventricular output, product of stroke volume and valve area	Time-consuming, poor repeatability, affected by shunts
Myocardial Performance Index (MPI)	Global measure derived from time intervals	Highly load-dependent, does not distinguish systolic / diastolic function
Systolic:Diastolic duration (SD:DD)	Time intervals obtained from outflow Doppler.	Heart-rate and load-dependent. Does not distinguish systolic and diastolic function
Tissue Doppler Imaging (TDI) of myocardial velocities	Longitudinal systolic and diastolic velocities measured in basal myocardium of RV, LV and septum.	Quantitative assessment of function. Angle- and load-dependent.
Ventricular strain assessed by Speckle Tracking Echocardiography (STE)	Quantitative assessment of global & regional deformation (strain, strain rate, twist) in multiples planes.	Specific hardware, software, user experience and optimal images. Inter-vendor differences.

Patel N et al. Seminars in Perinatol,2019

Prenatal heart

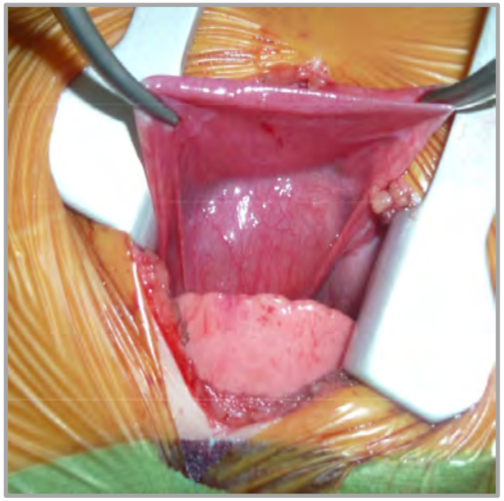
- Ventricular size as an outcome predictor *(Thebaud B et al, Intensive Care Med, 1997)* challenged by Vogel M *(2010)* et al. and Kailin et al. *(2017)* and confirmed by Byrne et al. *(2015)*
- Preferential streaming of the ductus and inferior cava vein towards de right hearth when liver is up *(Stressig R et al, Heart, 2010)*
- Speckle Tracking Echocardiography (STE)
  - Postnatal: Have demonstrated global systolic and diastolic LV dysfunction as well as abnormal synchrony of myocardial regions, associated with reduced left ventricular output *(Massolo AC et al, Neonatology 2019)*
  - Prenatal: No cardiac dysfunction *(DeKoninck P et al, Prenat Diagn, 2014)* *or limited to diastolic dysfunction* *(Cruz-Lemini et al, 2018)*
- Technically challenging (16% of insufficient quality) *(DeKoninck P)*

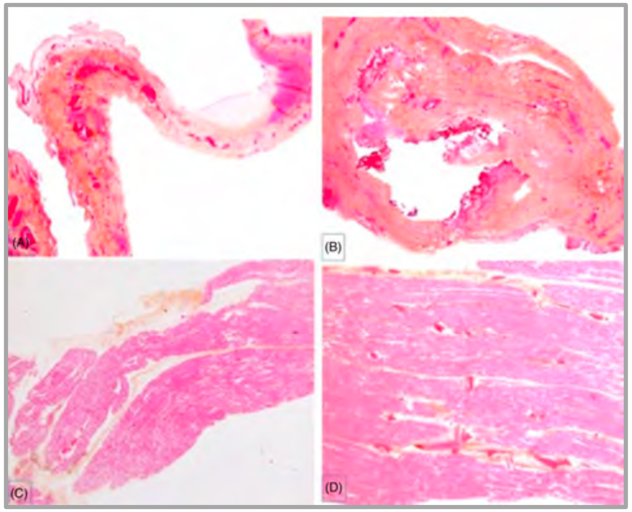
Diaphragmatic Sac

	% sac	Mortality	Oxygen dependency at 28 days	Time on ventimation	New	Comments
Bouchghoul H 2018	23% (17/86)	0/36% (p=0.03)	6/15% (p=0.33)	10.2/16.2d (p=0.32)	Suspected prenatal 33%	- Small series - Sac only
Oliver ER 2019	23% (46/200)	NA	43.9/59.2% (p=0.11)	15.5/23.5d p=0.04	Suspected prenatal 45.7% s /38.6 %(e)	Same incidence of GERD
Levesque M 2019	19.7% (14/71)	0/5.3% (p=1)	7.1/24.6% (p=0.27)	7.62±6.12 /15.9±19.2 (p=0.010)	Less vasoactive medication Less recurrence	- Small series - Exclude 9 surgery> 28d
Heiwegen K 2020	18% (19 s +17 e/200)	0/18% (p=0.03)	45% (s+e)/26% p=0.001	NA	More recurrence for s+e	- Include malformations - separated s+e

Diaphragmatic Sac

- Sac≉eventration
- Factors that may play a role in the observed differences
  - Sample size
  - Old cases included in large series
  - Management protocols (ECMO)
  - Sac + eventration





Bouchghoul H et al. Prenat Diagn, 2018

Diaphragmatic Sac

	Sensibility	Specificity	Positive Predictive Value	Negative Predictive Value
Meniscus of lung posterior or apical to the hernia contents	100% [29.2%-100%]	79.7% [68.7%-88.4%]	17.6% [3.8%-43.4%]	100% [93.5%-100%]
Encapsulated appearance of hernia contents	71.4% [41.9%-91.6%]	87.9% [76.7%-95.0%]	58.8% [32.9%-81.6%]	92.7% [82.4%-98.0%]
Presence of pleural fluid outlining a sac or ascites outlining a sac	75.0% [19.4%-99.4%]	79.4% [67.9%-88.3%]	17.6% [3.8%-43.4%]	98.2% [90.3%-100%]

Bouchghoul H et al. Prenat Diagn, 2018
Zamora IJ et al. AJR Am J Roentgenol, 2015

Prenatal brain anomalies ?

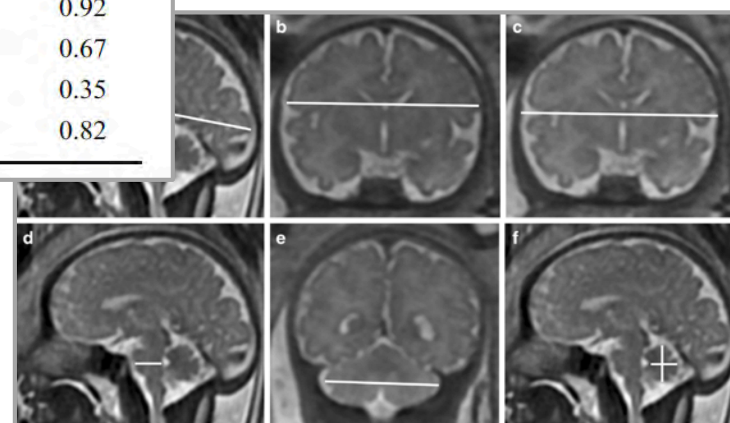
- Conditions affecting blood flow and perfusion of the brain such as congenital heart diseases can affect brain growth *(Limperopoulos C et al. Circulation, 2010)*
- Studies in CDH have focused on survivors and showed anomalies such as delayed brain maturation *(Danzer E etal. J Ped Surg, 2012)* or enlarged extraaxial spaces *(Radhakrishnan R et al. AJNR Am J Neuroradiol, 2017)*
- MRI-based brain volumetry in fetuses with CDH *(Prayer F et al, 27th ISUOG, 2017)*

Hôpitaux universitaires Paris-Sud

Prenatal brain anomalies ?

Brain morphometry	Gestational age	Survivor z-scores mean ± SD	Non-survivor z-scores mean ± SD	*t*-test *P*-value
Fronto-occipital diameter	<28 weeks	−0.03±1.66	0±1.55	0.95
	≥28 weeks	0.01±1.30	−0.03±1.46	0.93
Brain biparietal diameter	<28 weeks	−0.99±1.69	−0.52±1.48	0.35
	≥28 weeks	−0.67±1.77	−0.20±1.40	0.33
Bone biparietal diameter	<28 weeks	−0.29±1.55	−0.15±1.00	0.73
	≥28 weeks	0.09±1.56	0.02±1.33	0.88
Transverse cerebellar diameter	<28 weeks	0.33±0.97	0.16±0.94	0.55
	>28 weeks	0.01±1.27	−0.15±1.17	0.66
Anteroposterior cerebellar vermis	<28 weeks	−0.61±1.07	−0.78±1.09	0.60
	>28 weeks	−0.73±1.50	−1.91±1.74	0.02*
Craniocaudal cerebellar vermis	<28 weeks	−0.05±0.92	−0.02±1.47	0.92
	≥28 weeks	−0.45±1.71	−0.23±1.69	0.67
Anteroposterior pons	<28 weeks	−0.87±1.44	−1.27±1.31	0.35
	≥28 weeks	−0.81±1.16	−0.89±1.08	0.82

Correlation with o/e TLV



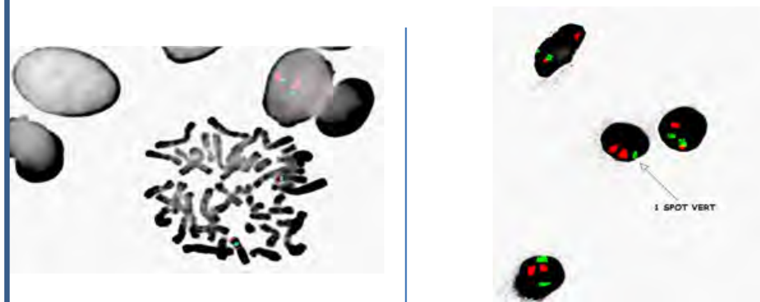
- Enlarged extraaxial spaces (57% > 28 weeks, 60% survivors/53% non survivors, p=0.77)
- Venous sinus distention *(23%/35% > 28 w, p=0.38)*

Radhakrishnan R et al. Pediatric Radiology, 2019

Prenatal brain anomalies ?

- Venous hypertension by impaired central venous return of cardiac origin?
- Middle cerebral artery flow velocity lower in CDH/controls *(Van Mieghem T et al. Ultrasound Obstet Gynecol, 2010)*
  - MCA pulsatility index unchanged
  - Cranial biometry and cerebral volume in CDH normal
- Clinical significance?

Genetics and Cytogenetics



CEP 12 (V) + locus spécifique 12p (O)

12p (V) / 12q (O)

- Array-comparative genomic hybridization (a-CGH) *on uncultured cells*
- First trimester diagnosis
  - CVS
  - But if others US anomalies (hydramnios, rhizomelic limb shortening, ventriculomegaly, nuchal fold, maternal age) → amniocentesis
- Pallister Killian syndrome
  - Tissue limited mosaicism for isochromosome 12p
  - Rapid decrease of the supernumerary marker isochromosome during culture

Salzano E et al. Am J Med Genet, 2018 - Frisova V et al, Taiwanese J Obstet Gynecol, 2018
Doray B et al, Prenat Diagn, 2002- Struthers JL et al, Am J Med Genet, 1999

What's next?

- O/E LHR, Liver and TLV at MRI measurements
- Sac and eventration diagnosis
- Need for studies on right CDH
- Intra-parenchymal pulmonary vascularisation evaluation
- Prenatal heart and brain evaluation