Università degli Studi di Padova
Dipartimento di Scienze Ginecologiche e della Riproduzione Umana
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

Ernia Diaframmatica Congenita: Antenatal Management

- ***Dott.ssa A. Cacace***

UNIVERSITA' DEGLI STUDI DI PADOVA
DIPARTIMENTO DI SALUTE DELLA DONNA E DEL BAMBINO
SCUOLA DI SPECIALIZZAZIONE IN GINECOLOGIA ED OSTETRICIA
Direttore: Prof. G.B. Nardelli

Sig.ra C. F. 32 aa

- UM: 17/10/2013 EA 25+5 SG
- PARA 0010

  – An Familiare: ndp
  – An Fisiologica: 1 aborto spontaneo a 6 SG (no RCU)
  – An Pat Remota: ndp

Sig.ra C. F.

- **Ecografia del 1 trimestre** (12+2SA)
  - Ecografia:
    - CRL = 61 mm ; NT = 0.9 mm
  - Makers sierici :
    - βhCG = 1.45 MoM ; PAPP-A = 0.8 MoM
  - Rischio combinato: 1/4500

- **Ecografia del 2 trimestre** (22+2SA)

  Morfologia fetale indagata nella norma

  LA aumentato senza polidramnios

Sig.ra C. F.

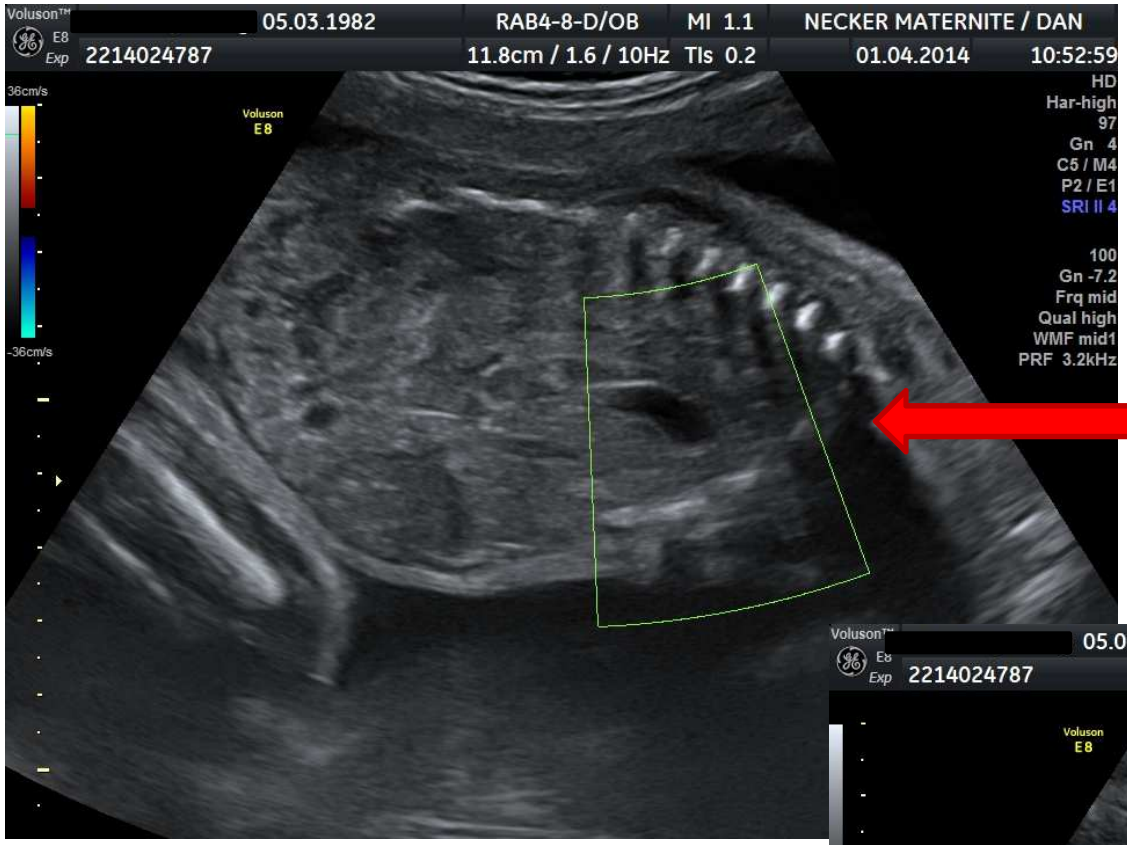
- **Ecografia di controllo** (25+4SA)

  Polidramnios

  Sospetta ernia diframmatica destra isolata

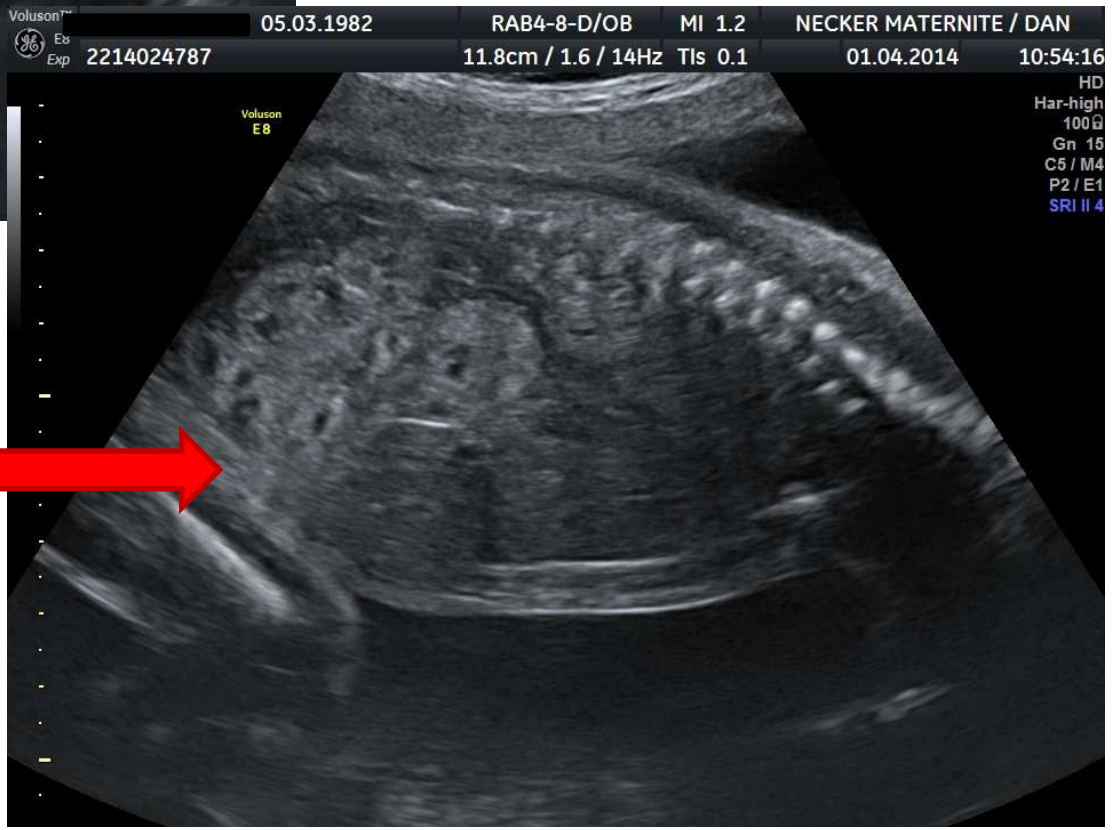
- **Ecografia di II livello** (25+5 SA)

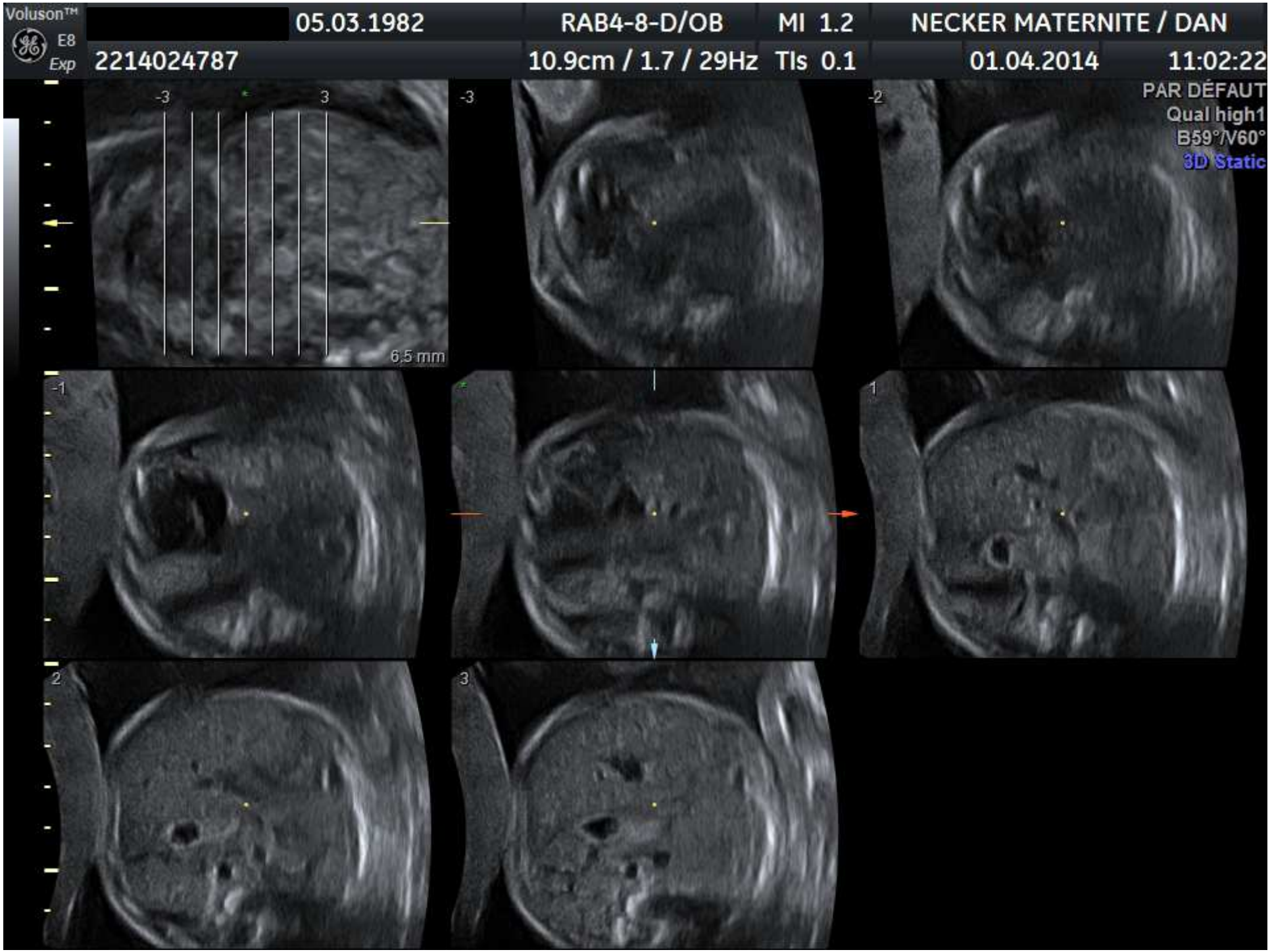
  Ernia diaframmatica destra contenete una parte di fegato, che appare mediano, dell'intestino e la colecisti con shift mediastinico e spostamento del cuore sinistra. LHR=1.8

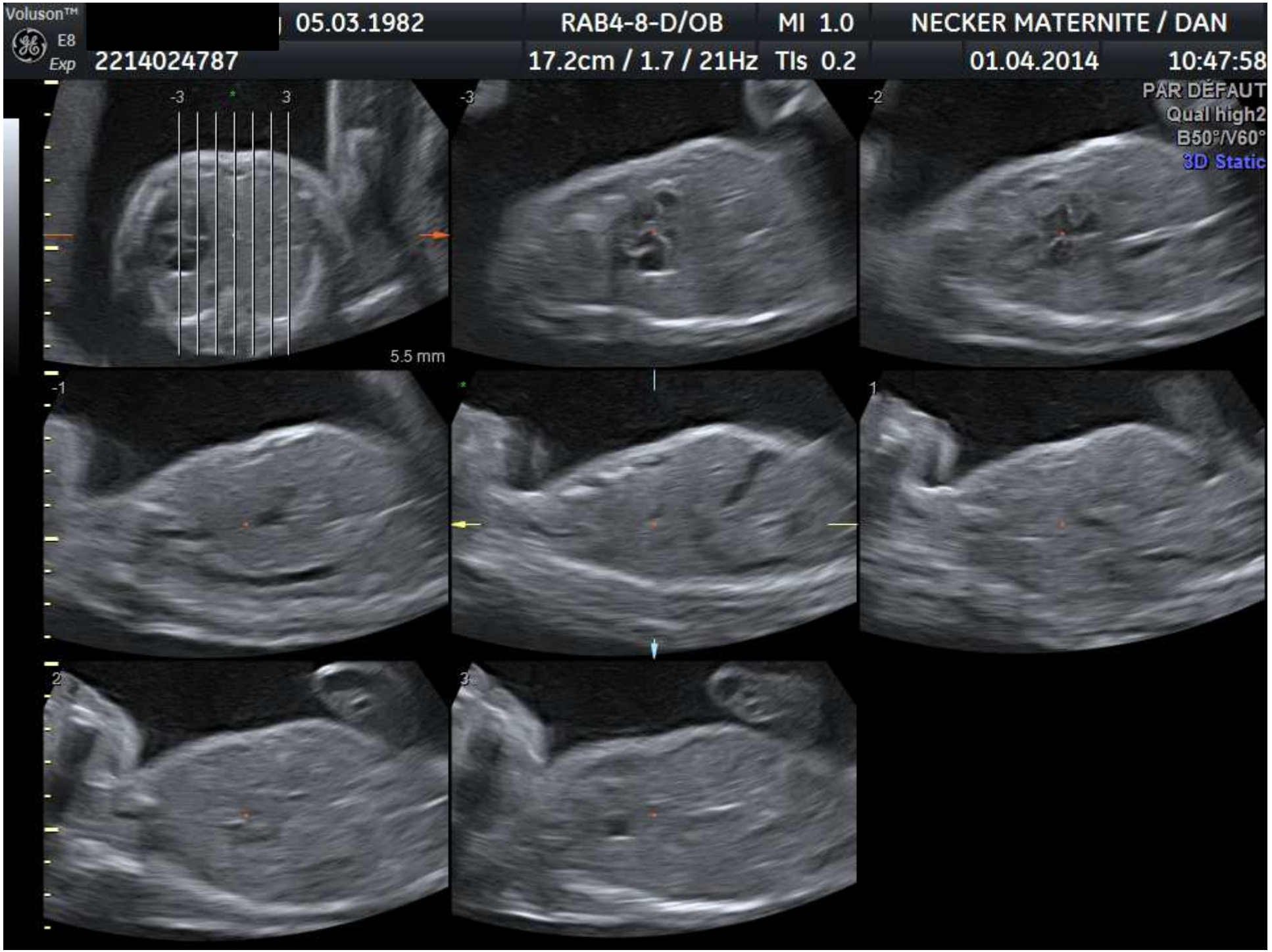


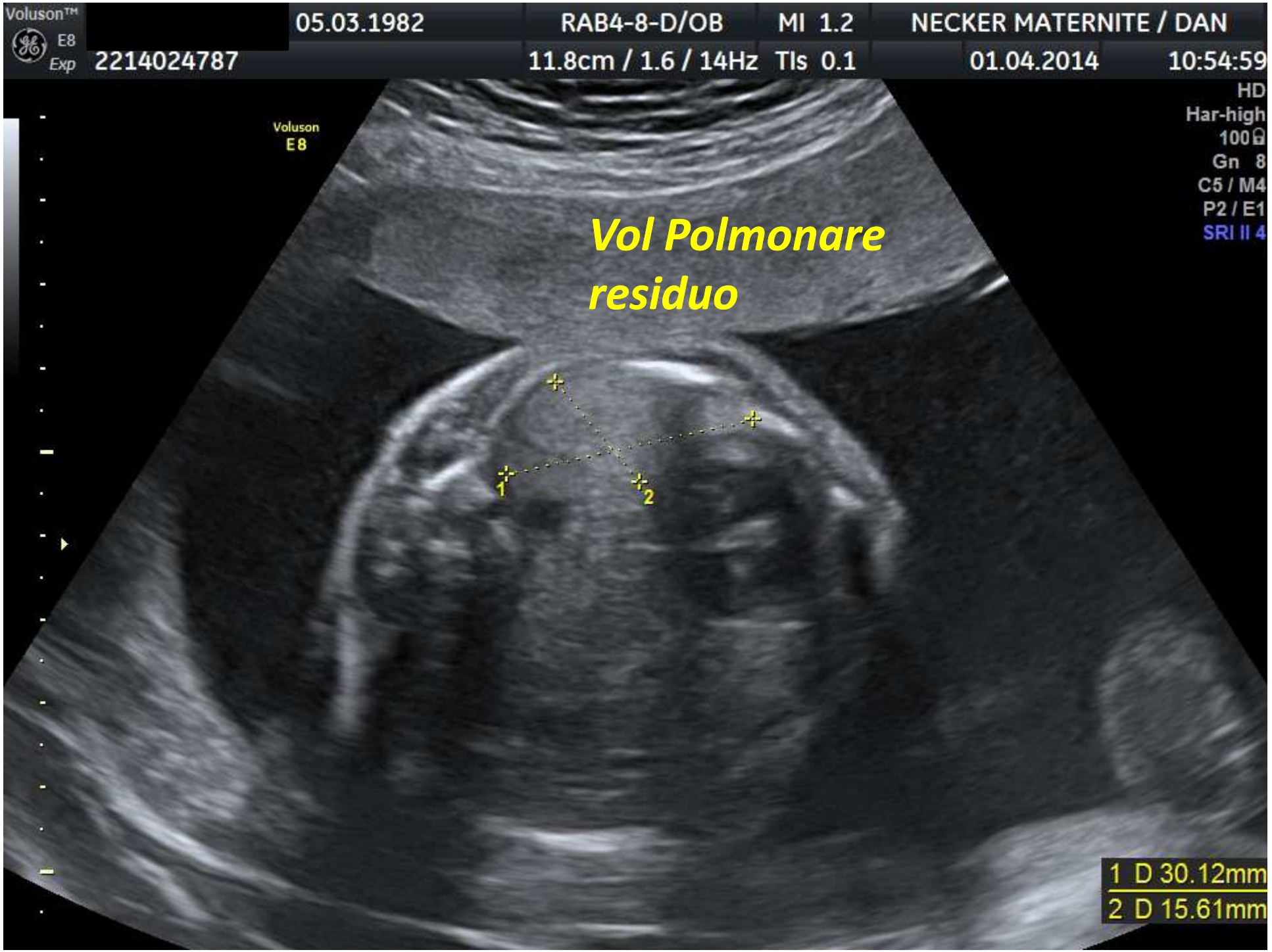
colecisti

Intestino e fegato in torace




Voluson™
E8
Exp
05.03.1982
RAB4-8-D/OB
MI 1.2
NECKER MATERNITE / DAN
2214024787
10.9cm / 1.7 / 29Hz
TIs 0.1
01.04.2014
11:02:22
PAR DÉFAUT
Qual high1
B59°/V60°
3D Static
-3
3
6,5 mm
-3
-2
-1
1
2
3


Voluson™
E8
Exp
05.03.1982
RAB4-8-D/OB
MI 1.0
NECKER MATERNITE / DAN
2214024787
17.2cm / 1.7 / 21Hz
TIs 0.2
01.04.2014
10:47:58
PAR DÉFAUT
Qual high2
B50°/V60°
3D Static
5.5 mm


Voluson™
E8
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RAB4-8-D/OB
MI 1.2
11.8cm / 1.6 / 14Hz
TIs 0.1
NECKER MATERNITE / DAN
01.04.2014
10:54:59
HD
Har-high
100
Gn 8
C5 / M4
P2 / E1
SRI II 4
Voluson
E8
Vol Polmonare
residuo
1
2
1 D 30.12mm
2 D 15.61mm

Sig.ra C. F.

- **Esami complementari** :

  Amniocentesi

  - Cariotipo maschile normale

  - CGH Array normale

  Ecocardiografia fetale

  - nella norma

  RMN

  - in programma

Sig.ra C. F.

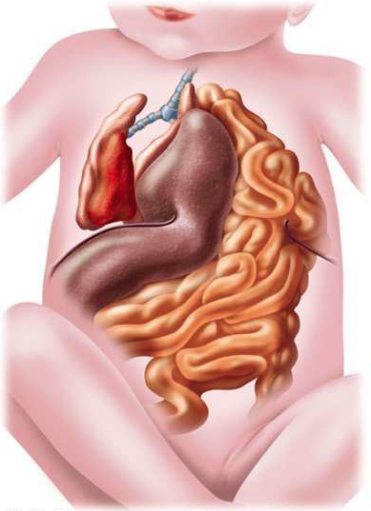
- **Inviata per:**
  - Sospetta ernia diaframmatica destra con polidramnios
- **Diagnosi:**
  - Ernia diaframmatica destra isolata con shift mediastinico e spostamento del cuore a sinistra.
- **Esami complementari:**
  - Amniocentesi, ecocardiografia fetale, RMN
- **Condotta:**

- Consulenza chirurgca pediatrica
- Controllo ecografico settimanale

CDH

- DEF: Erniazione dei visceri addominali nel torace fetale derivante da un difetto congenito del diaframma per mancata chiusura del canale pleuroperitoneale tra la 6 e la 12 SG
- Incidenza: 1/2500 nati vivi
- 8% di tutte le anomalie congenite
- Età gestazionale media alla diagnosi 24 SG
- 60% isolate
- 40% anomalie associate
  - 10-20% anomalie cromosomiche (13,18,21)
  - 10% sindromi plurimalformative

  (Fryns, CHARGE, Goldenhar, Beckwith Wiedemann..)
  - anomalie associate:
    - difetti del tubo neurale
    - cardiopatie
    - linea mediana (atresia esofagea, cleft palatino)


© UZ Leuven

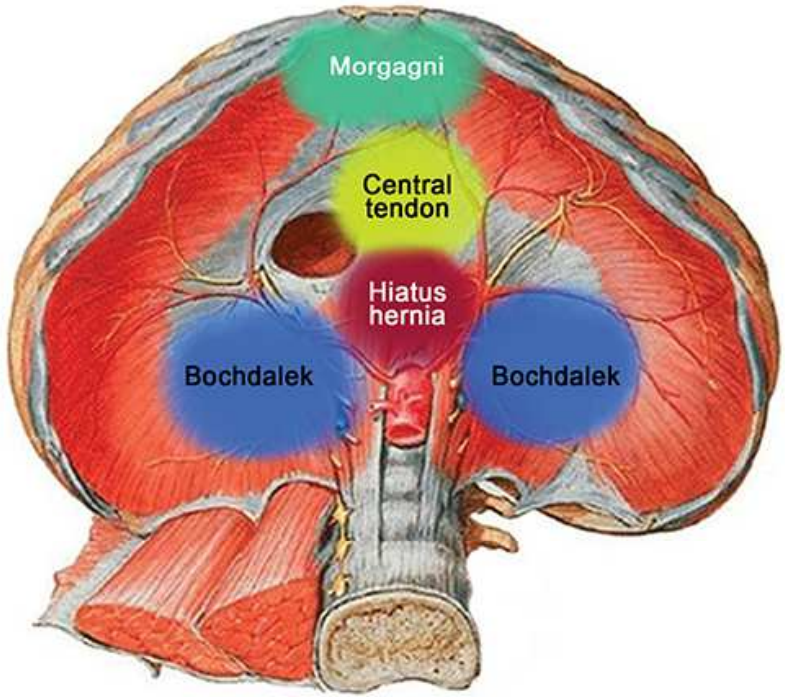
CDH

- 85% Posterolaterali (di Bochdalek)

parte post del diaframma è l'ultima a formarsi

➡ *+freq!*

- Sinistra 84%
- Destra 13 %
- Bilaterali < 2%



- 13% Anteriori o retro-parasternali (di Morgagni)

- < 2% Centrali

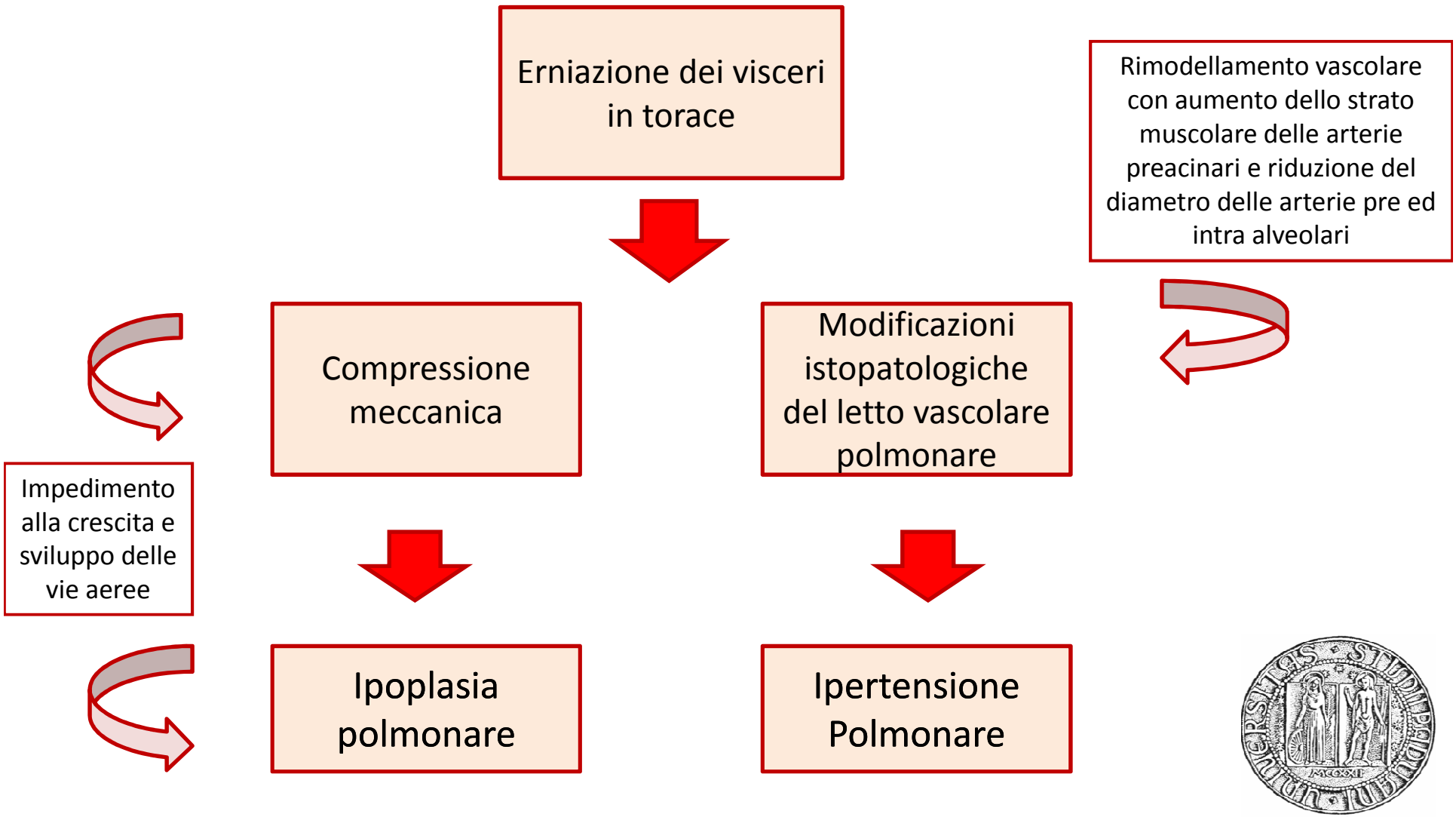
(a livello del centro tendineo del diaframma)

- Eventrazione diaframmatica

- Agenesia del diaframma

CDH

PATOGENESI



CDH - OUTCOME

- Sopravvivenza

  CHD associata ad altre anomalie

  ➡ *85% mortalità neonatale*

  CDH isolata

  ➡ *30% mortalità neonatale*

  (varia a seconda dei sottogruppi prognostici in base a volume polmonare residuo ed erniazione del fegato in torace)

- Morbidità

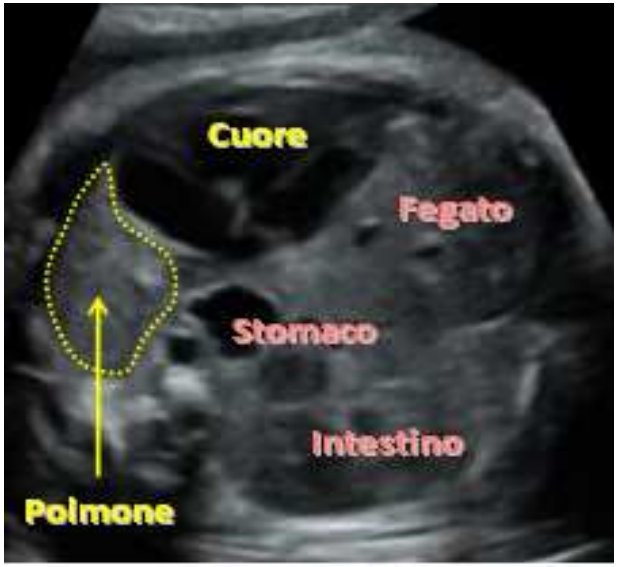
legata alla ipoplasia e ipertensione polmonare:

- insuff ventilatoria

- ipertensione polmonare

necessità di patch postnatale per difetti di grandi dimensioni

problemi gastrointestinali (reflusso gastroesofageo)



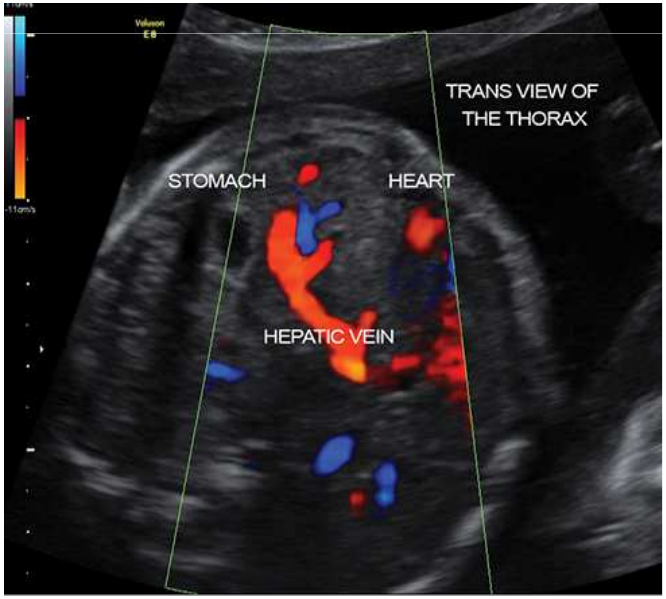
USG: ernia diaframmatica sx

DIAGNOSI PRENATALE

ECOGRAFIA

Sospetto ernia diaframmatica:

➡ mancata visualizzazione della cupola diaframmatica



E' importante:

1. Escludere anomalie morfologiche associate
2. Visualizzare i visceri erniati in torace
3. Erniazione del fegato intratoracico
4. Valutare entità shift mediastinico
5. Misurare area polmonare residua (LHR)

CDH - DIAGNOSI PRENATALE

ECOGRAFIA

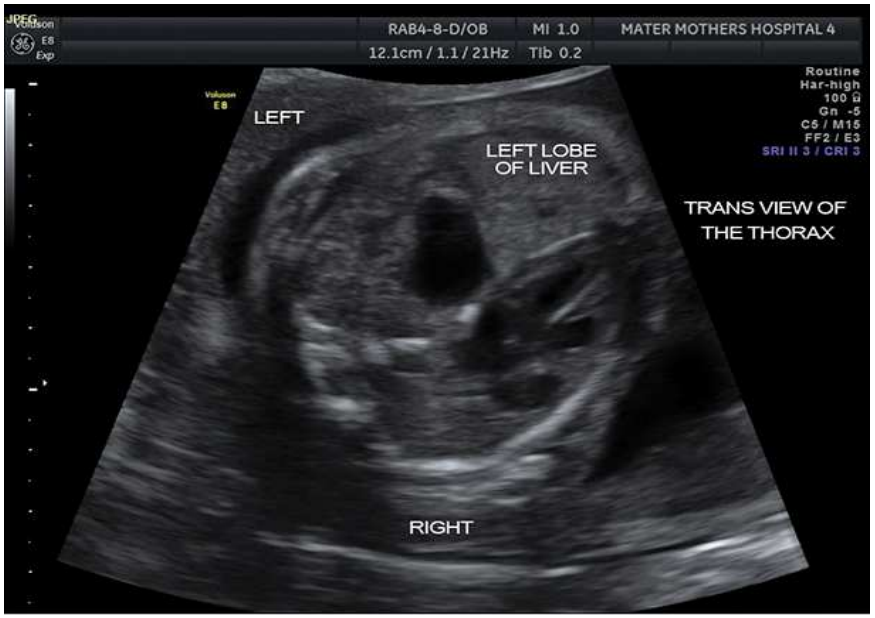
ERNIA SINISTRA

Erniazione di stomaco in torace

Parte di intestino

Lobo sinistro del fegato

Shift mediastinico a dx



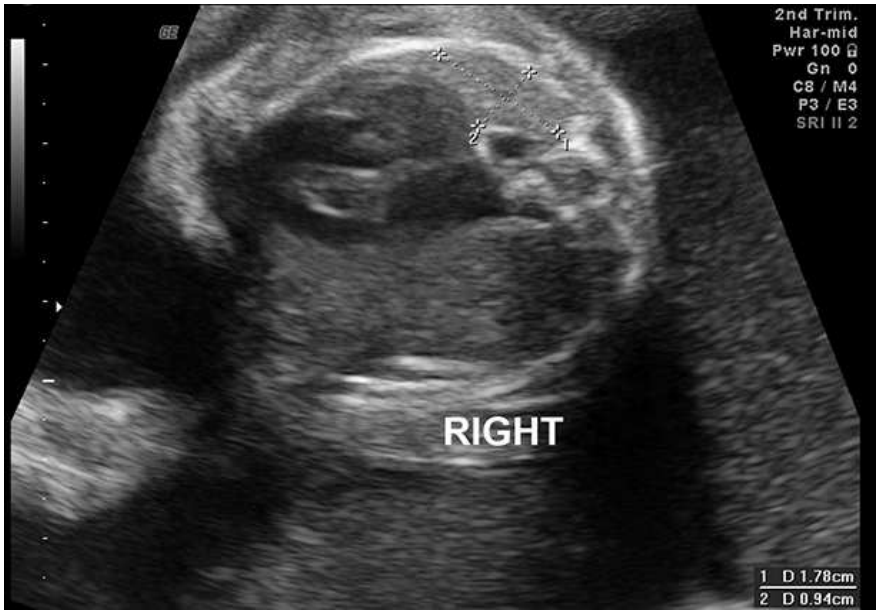
ERNIA DESTRA

Erniazione di fegato in torace

Visualizzazione della colecisti

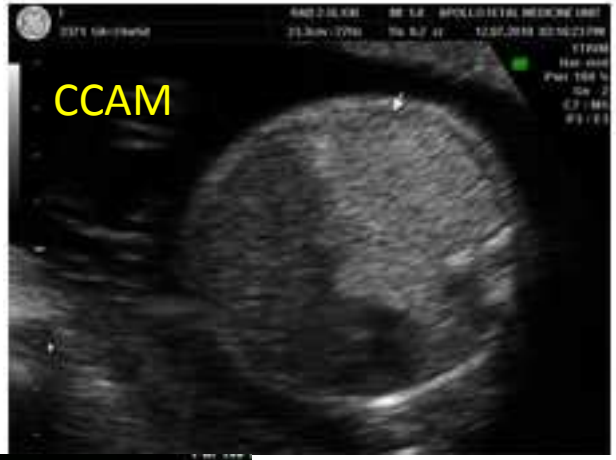
Dislocazione delle vene epatiche

Shift mediastinico a sx



CDH – DIAGNOSI DIFFERENZIALE

- CCAM
- Sequestro bronco-polmonare
- Cisti Broncogene
- Atresia bronchiale
- Cisti enteriche
- Teratomi



Misura dell'area polmonare residua

LHR *(Lung-to-Head-Ratio)*

3 metodi:

A livello della scansione 4 camere

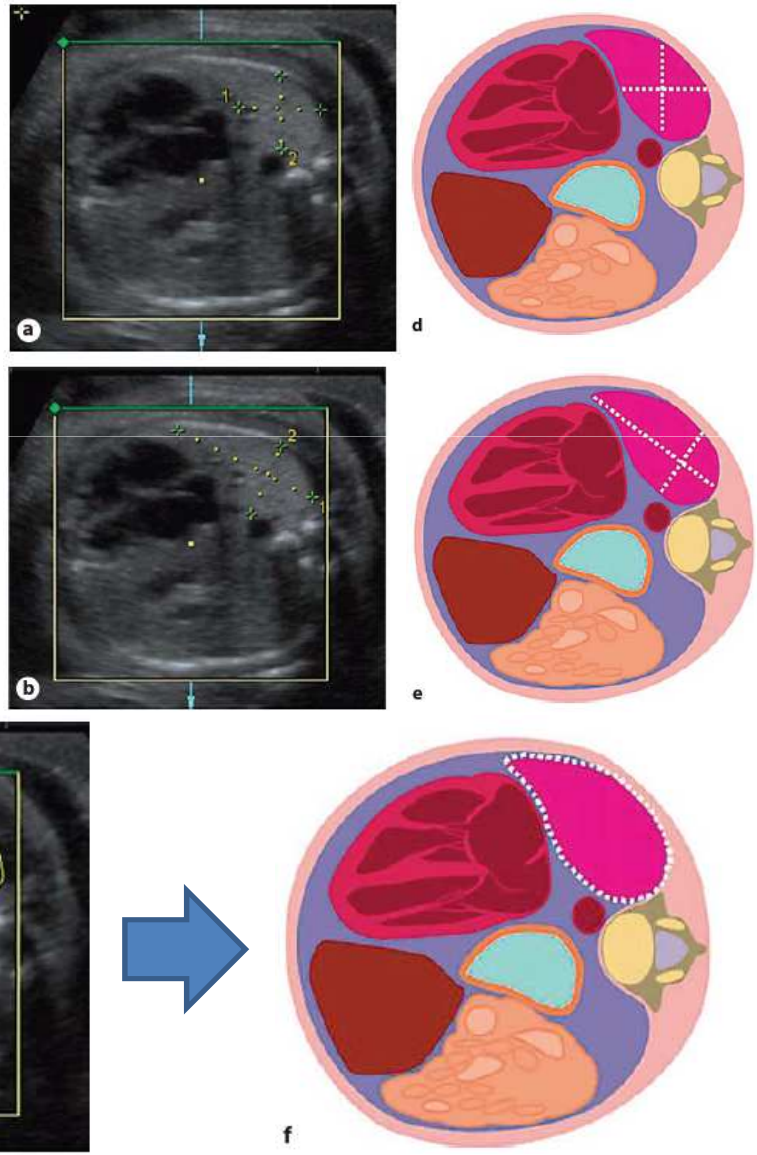
1. Diametro A-P x L-L

(a livello del punto medio del precedente)

(Metkus et al. 1996)

2. Diametro polmonare maggiore x diametro ad esso perpendicolare

3. Traccia manuale del contorno polmonare



Miglior sima dell'area polmonare residua

(Peralta et al. 2005)

Misura dell'area polmonare residua

LUNG-TO-HEAD-RATIO (LHR)

$$\frac{\text{area polmonare controlaterale (mm2)}}{\text{CC (mm)}}$$

Ma…dipende dall' età gestazionale

tra 12 e 32 SG l'area polmonare cresce 4 volte di più rispetto alla CC (Peralta et al. 2005)

Observed/Expected LHR

Ad oggi ancora migliore indice prognostico!

www.totaltrial.eu
Official calculator

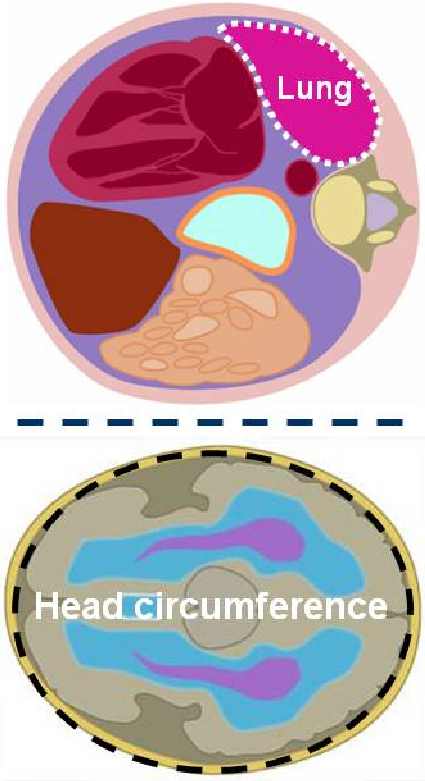


Table 1

Formulas for calculating the expected LHR of the right lung, i.e. the value one expects in a normal fetus based on its gestational age. There is a formula specific for each measurement method; we have left out the least accurate anterior–posterior method. The prediction formulas are based on observations made in 650 fetuses between 12 and 32 weeks of gestation at the Harris Birthright Centre for Fetal Medicine. We thank Dr. Peralta and Prof. Nicolaides for providing these formulas which were recalculated using the raw data on our request, and were also used in the web-based calculator displayed on www.totaltrial.eu. One can express the gestational age in weeks or weeks plus days (converted to one decimal).

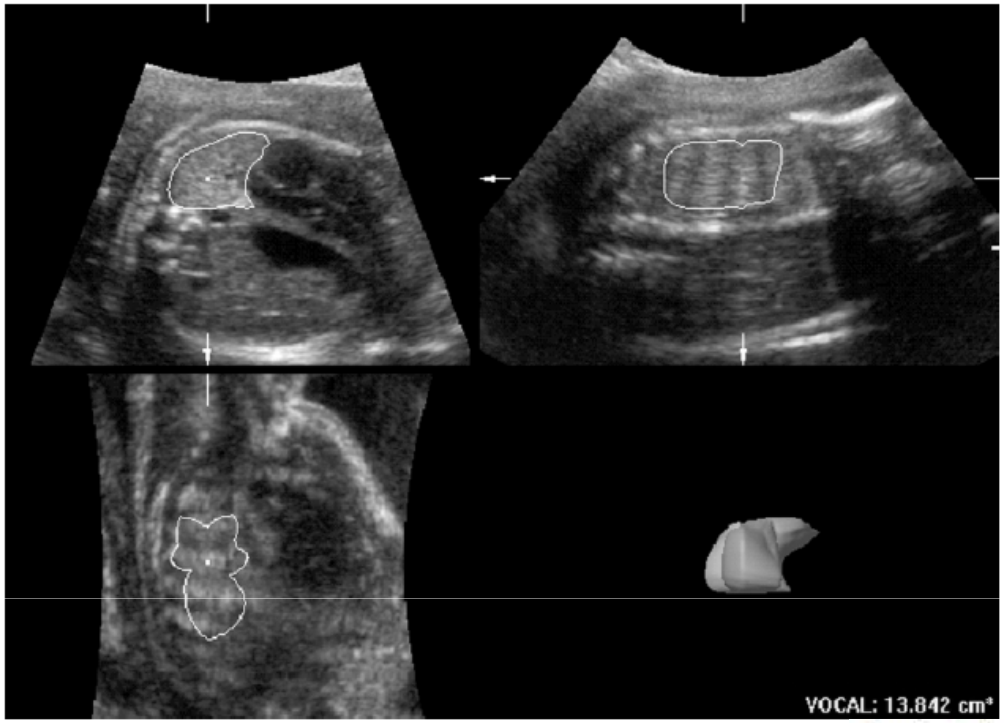
When using gestational age (GA) expressed in entire weeks		When using gestational age (GA) expressed in weeks and days (converted to number with one decimal value as below in last line of the table)	
Tracing method	Longest axis method	Tracing method	Longest axis method
$-2.218+(0.268\times GA(wks))+(-0.003\times GA(wks)^2)$	$-3.314+(0.397\times GA(wks)-0.004\times GA(wks)^2)$	$-2.356+(0.272\times GA(wks.dec)-0.003\times GA(wks.dec)^2)$	$-3.480+(0.399\times GA(wks.dec)-0.004\times GA(wks.dec)^2)$

Conversion of days to decimals	0 d = 0.00	1 d = 0.14	2 d = 0.29	3 d = 0.43	4 d = 0.57	5 d = 0.71	6 d = 0.86

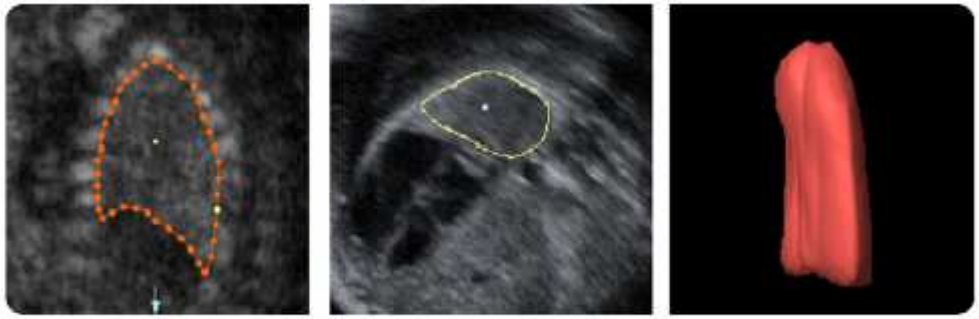
Misura dell'area polmonare residua

ECO 3D

- Bilateral (total) lung volume
- 40% misurazione polmone omolaterale impossibile
  => RMN
- Fattori che interferiscono con la tecnica 3D
- LHR *(2D US)*
  - più facilmente riproducibile
  - più accurato nella stima del volume polmonare



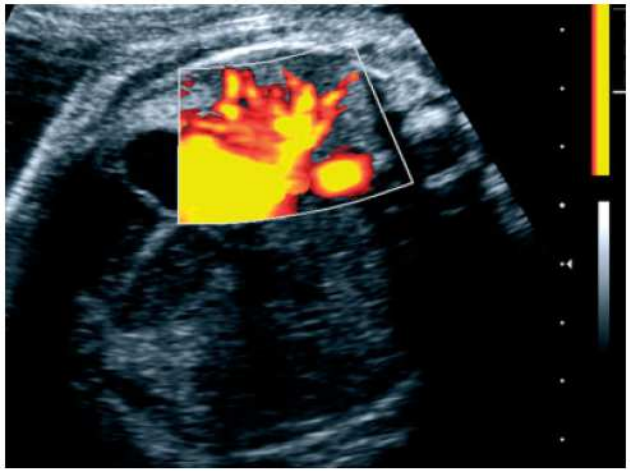
Jani et al.
Ultrasound Obstet Gynecol 2007; **30**: 850–854.



Measurement of the right lung volume using the rotational technique (VOCAL) in a fetus with left-sided diaphragmatic hernia. The picture on the left represents the starting plane of rotation of

Peralta. Fetal lung volume after FETO and postnatal outcome. Am J Obstet Gynecol 2008.

CDH - DOPPLER



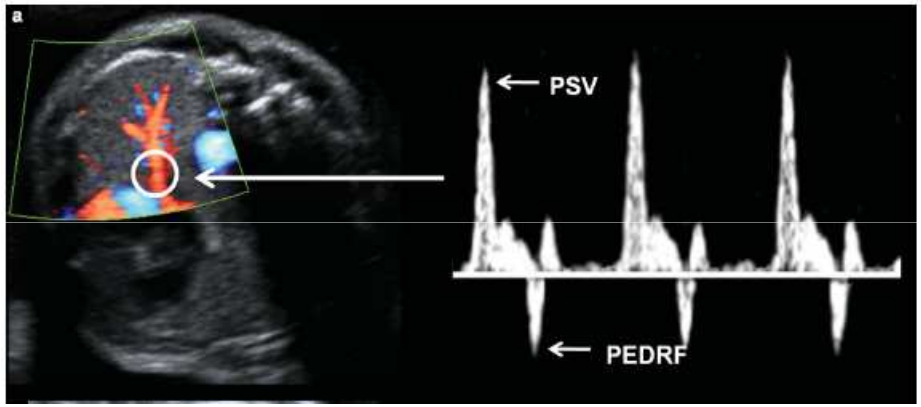
1. Valutazione perfusione tessuto polmonare

   FMBV: fractional moving blood volume

   aumento proporzionale a O/E LHR

(Moreno –Alvarez U Ob Gyn 2010)

2. Studio Doppler-flussimetrico della diramaz prox dell'arteria polm controlat



   - PI: pulsatility index

     anormale nel polmone omolaterale

     nel gruppo a prognosi peggiore

   - PEDRF: peak early diastolic reversed flow

     correla inversamente con LHR in entrambi i polmoni *(aumento resistenza vascolare)*

(Moreno-Alvarez, UOG 2008)

PEDRF = possibile indice di ipertensione polmonare !

O/E LHR resta indice prognostico più significativo
ma parametri Doppler-flussimetrici utili -*soprattutto nei pz a prognosi peggiore (LHR <25%)*- a discriminare sottogruppi prognostici

(Cruz-Martinez et al.,Ultrasound Obstet Gynecol 2010)

CDH - MANAGEMENT

Sospetto ecografico:

1. Cariotipo fetale
2. Ecocardiografia fetale *(escludere anomalie associate e valutare segni di scompenso, dimensioni delle 4camere)*
3. RMN
4. Consulenza genetica
5. Consulenza chirurgica pediatrica

Monitoraggio della gravidanza:

- monitoraggio ecografico ogni 15 gg a partire da 28 SG
- NST bisettimanali da 33-34 SG *(ACOG guidelines)*

Modalità e Timing del parto:

- Induzione del travaglio di parto a 37-38 SG presso un centro di III livello
- Non è stato dimostrato un vantaggio in termini di sopravvivenza e morbidità in neonati nati da TC vs parto vaginale *(Frenckner et al, J Pediatr Surg 2007)*

CDH - Cariotipo fetale

- Escludere anomalie cromosomiche (Tri 13, 18, 21) associate a prognosi peggiore
- Maggior parte delle aberrazioni cromosomiche e anomalie genetiche sono *sporadiche , mutazioni de novo*

Identification of dosage-sensitive genes in fetuses referred with severe isolated congenital diaphragmatic hernia

P. D. Brady[1], P. DeKoninck[2,3], J. P. Fryns[1], K. Devriendt[1], J. A. Deprest[2,3] and J. R. Vermeesch[1]*

Prenatal Diagnosis 2013, 33, 1283–1292

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Genetic factors play an important role in non-isolated or syndromic congenital diaphragmatic hernia (CDH).
- The genetic causes of isolated CDH remain largely unknown.

Further use of chromosomal microarrays for the investigation of isolated CDH patients will continue to identify loci and genes that are involved in CDH. The combination of array analysis along with clinical outcome and long-term follow-up of survivors will allow for the determination of which submicroscopic CNVs are associated with a poor outcome.

WHAT DOES THIS STUDY ADD?

- Pathogenic submicroscopic copy number variations were identified in 9% of fetuses referred with apparently isolated CDH.
- The 15q26 CDH locus is refined, highlighting haploinsufficiency of NR2F2 as a cause of CDH and cardiovascular malformations.
- Evidence is provided for an association of 15q25.2 and 16p11.2 recurrent microdeletions with isolated CDH.
- Several novel dosage-sensitive CDH candidate genes are proposed.

CDH - RMN

Metodo di imaging complementare all'ecografia:

- limitazioni all' esame ecografico

(obesità materna, oligo/anidramnios, posizione fetale sfavorevole)

- aggiunta di informazioni prognostiche:

a. Sequenze T2 HASTE

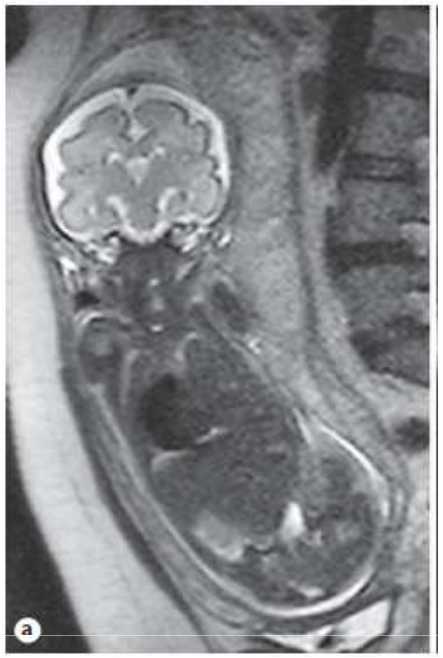
→ volume polmonare fetale

(ipsi e controlaterale e calcolo del volume polmonare totale TFLV)

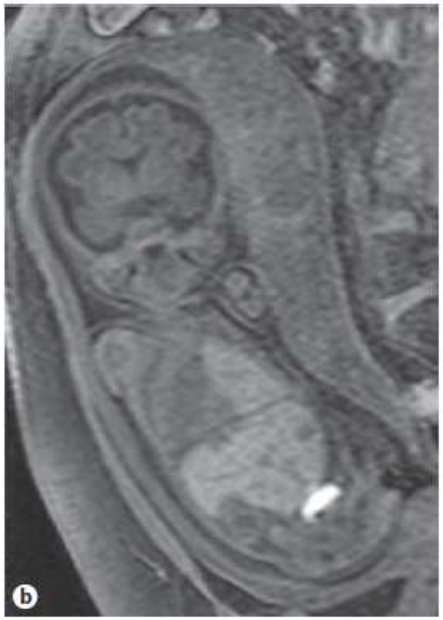
b. Sequenze T1

→ valutazione visceri erniati

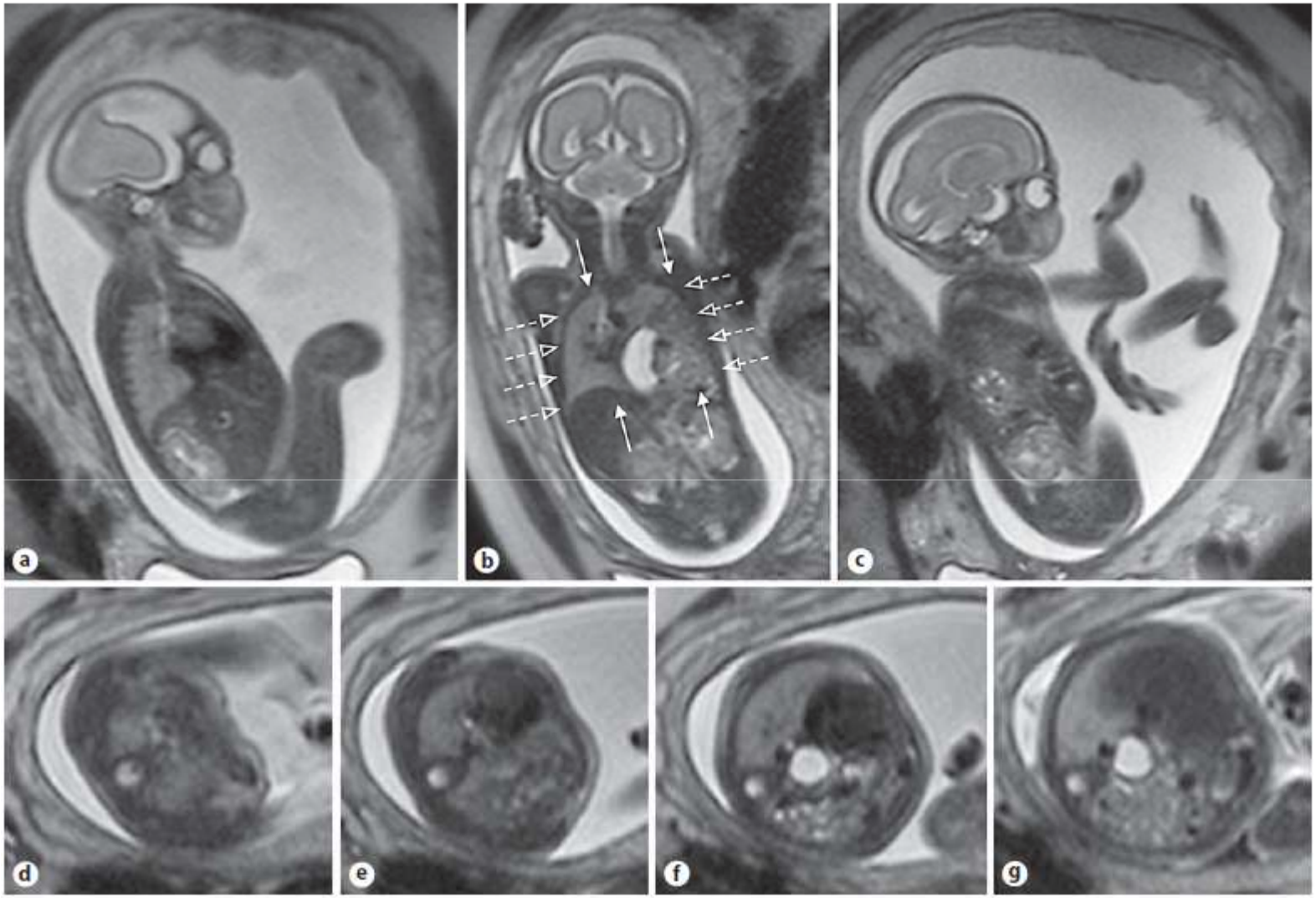
→ *quantificazione* erniazione del fegato



a. T2; b. T1 «Liver up»



CDH - RMN



Le frecce continue indicano le scansioni sagittali, le frecce tratteggiate le scansioni assiali sottostanti.

F. Claus et al.
«Prenatal anatomical imaging in fetuses with CDH»
Fetal Diagn Ther2011

CDH - RMN

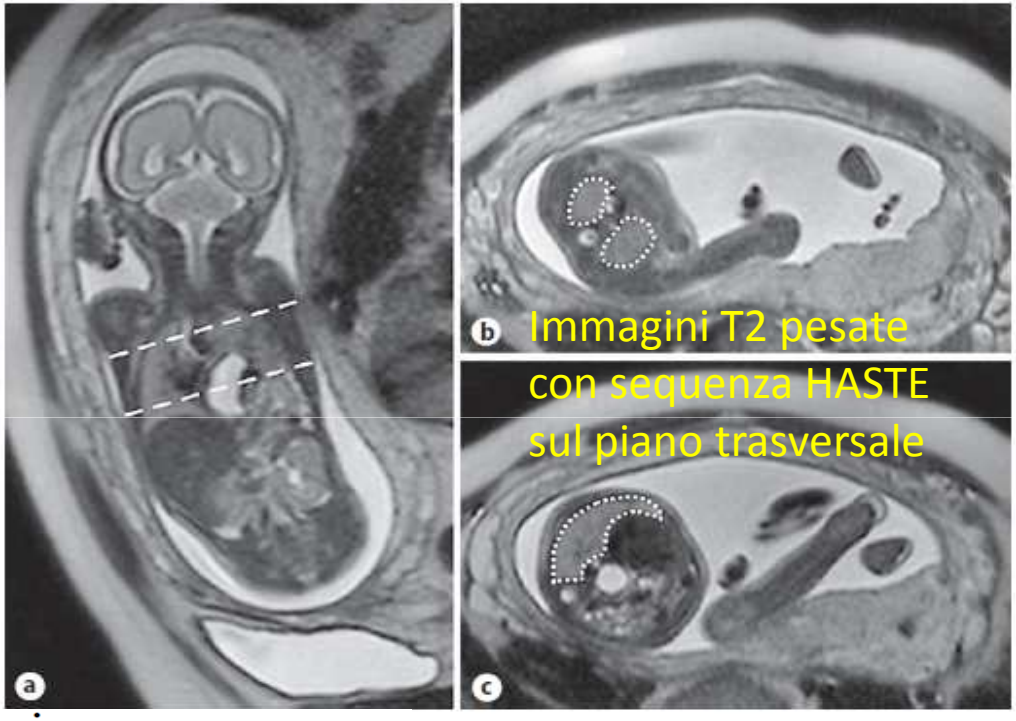
Ultrasound Obstet Gynecol 2007; 30: 855–860

Relationship between lung area at ultrasound examination and lung volume assessment with magnetic resonance imaging in isolated congenital diaphragmatic hernia

J. JANI*, M. CANNIE†, E. DONE*, T. VAN MIEGHEM*, D. VAN SCHOUBROECK*, L. GUCCIARDO*, S. DYMARKOWSKI† and J. A. DEPREST*

In conclusion, measurement of the contralateral lung area using the longest axis method by 2D ultrasound examination provides a good estimate of the total FLV, as measured by MRI.

F. Claus et al.
«Prenatal anatomical imaging in fetuses with CDH»
Fetal Diagn Ther2011



Sequenze T2 HASTE

→ volume polmonare fetale (ipsi e controlaterale e calcolo del volume polmonare totale TFLV)

- Correla con LHR-

Value of prenatal magnetic resonance imaging in the prediction of postnatal outcome in fetuses with diaphragmatic hernia

Ultrasound Obstet Gynecol 2008; 32: 793–799

J. JANI*†**, M. CANNIE†, P. SONIGO‡, Y. ROBERT§, O. MORENO¶, A. BENACHI‡ E. GRATACOS¶, K. H. NICOLAIDES* and J. DEPREST†

Conclusions In the assessment of fetuses with CDH, MRI-based o/e TFLV is useful in the prediction of postnatal survival.

We have also shown a trend towards a better prediction with o/e TFLV by MRI rather than with o/e LHR measured by 2D ultrasound examination; this should

CDH - RMN

Quantification of intrathoracic liver herniation by magnetic resonance imaging and prediction of postnatal survival in fetuses with congenital diaphragmatic hernia

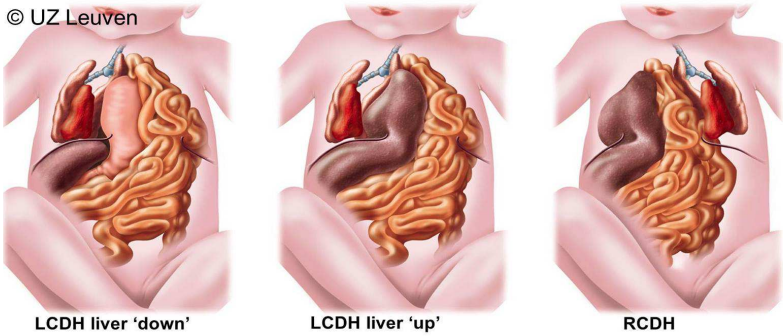
M. CANNIE*¶, J. JANI†** , C. CHAFFIOTTE‡, P. VAAST§, P. DERUELLE§, V. HOUFFLIN-DEBARGE§, S. DYMARKOWSKI* and J. DEPREST†

Ultrasound Obstet Gynecol 2008; **32**: 627–632

LiTR

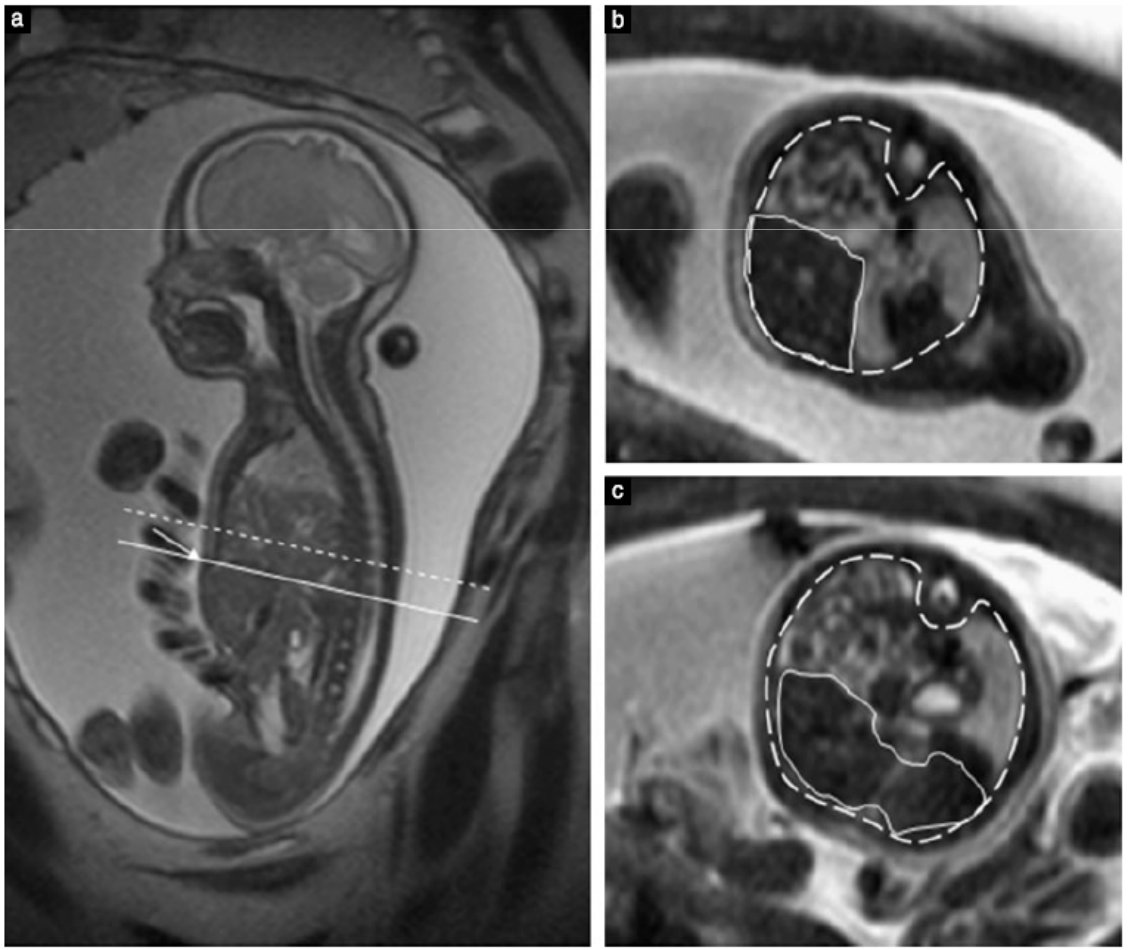
Volume fegato erniato
Volume cavità toracica

DATO QUANTITATIVO
Vs
Variabile categorica
("Liver Up" o "down")



→ *Fattore prognostico indipendente dal TFLV…*

….ma ancora non chiaro il valore prognostico del dato quantitativo!



CDH - Prognosi

Fattori prognostici negativi:

- Cariotipo alterato/malformazioni associate
- Età precoce alla diagnosi (<25sg)
- Polidramnios
- LHR <1 ; O/E LHR <25%; TFLV <25%

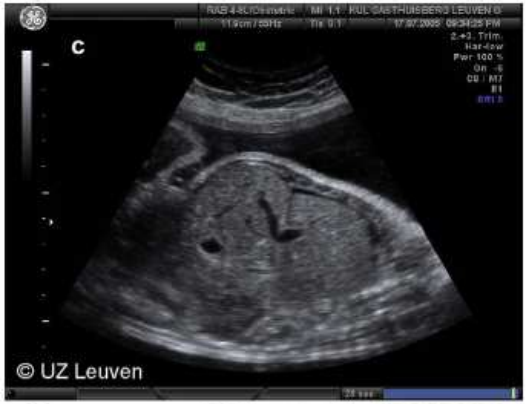
  (Metkus 1996;Deprest 2009; Jani UOG 2008)
- Erniazione epatica

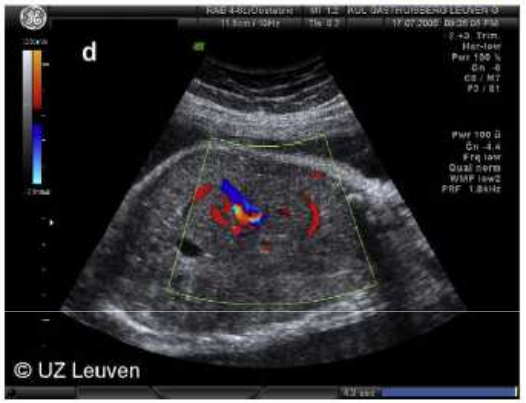
  (Jani UOG 2008; Deprest 2009; Mayer 2011)
- Shift mediastinico severo

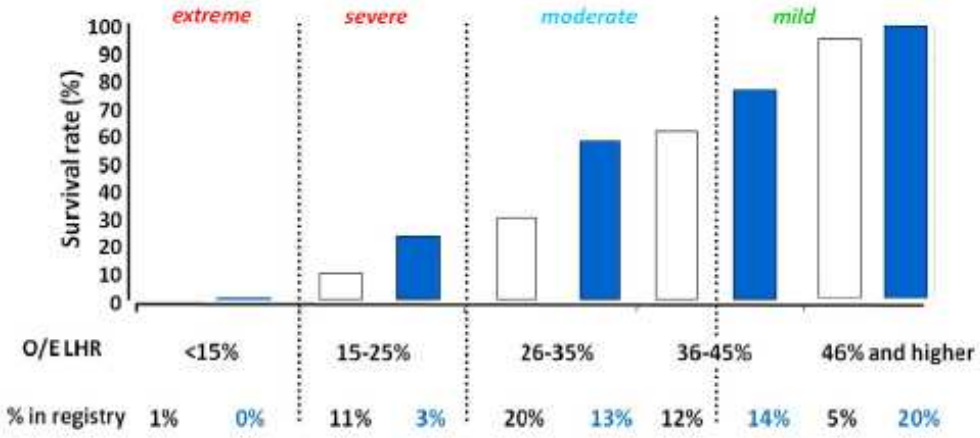
  => polmone controlat piccolo

  => ipoplasia Vsx

  (Van Mieghem, UOG 2009)







(Deprest et al, Sem Fetal Neonat Med 2009) liver in thorax ("up") liver in abdomen ("down")

Fig. 1 Survival rates of fetuses with isolated left-sided CDH, depending on the measurement of the O/E LHR and the position of the liver as in the antenatal CDH registry. Numbers at the bottom refer to the number in each severity group. Adapted from Deprest et al [19], with permission of the authors and the publisher.

CDH – Terapia fetale

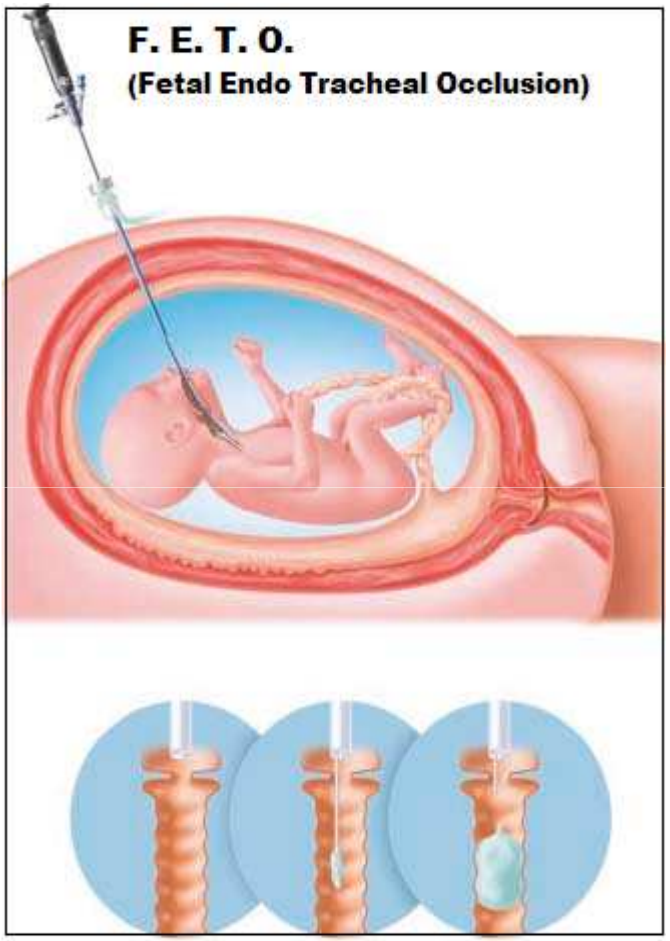
- Late 1980s anatomical repair for fetuses "Liver down" *(Harrison 1981-1990)*
- 1990s First raised concept of tracheal obstruction PLUG
  (Di Fiore 1994; Hedrick 1994)
- 1995 Fetoscopic TO with endoluminal balloon in lambs *(Deprest)*
- 1996 TO with metal clips *(Harrison)*
- 2000
  - TO by Laparotomy hysterotomy neck dissection tracheal clipping *(Flake)*
  - First percutaneous endoluminal occlusion– failed *(Quintero)*
- 2001 Laparotomy for uterine exposure + Fetoscopic 4,5 mm single port
  (Harrison)
- 2002-2004 In Europe: Fetal Endoscopic Tracheal Occlusion – FETO Task Force
  (Bouchard 2002; Deprest 2004)

SCOPO:
- Impedire la fuoriuscita delle secrezioni fluide prodotte nelle vie aeree fetali
- il liquido si accumula nel polmone fetale, aumenta la pressione nelle vie aeree e ne permette così l'espansione
- conseguente crescita e sviluppo del letto vascolare

Figure 6—One of the first fetoscopic endoluminal tracheal occlusion procedures in 2001, performed by the FETO consortium, with Jan Deprest, Eduardo Gratacos and Kypros Nicolaides (from left to right). Courtesy: Geo Magazin, Germany, Dr A Vinciano. © Thomas

CDH - TERAPIA FETALE

F.E.T.O. (Fetal Endoscopic Tracheal Occlusion)



Percutaneo = mini-invasivo

Metodo:

1. Anestesia regionale + locale, analgesia e immobilizzazione fetale *(fentanyl,pancuronio e atropina)*
2. Cannula 3,3 mm flessibile in teflon introdotta in cavità amniotica
3. Visualizzazione della bocca fetale e introduzione degli strumenti endoscopici
4. Inserimento e gonfiaggio del balloon in trachea a livello della carena

Timing:

-Inserimento del balloon a 26-28 SG
(solo CDH severe: LHR <1 e "liver up")

-Rimozione ideale a 34 SG mediante fetoscopia (50%) o puntura ecoguidata con ago 20 G (19%)
maturazione polmonare ⇒ TO persistente riduce in n° di pneumociti II e quindi la produz di surfactant!
parto vaginale

- Rimozione al momento del parto in caso di parto pretermine (EXIT 21%, tracheoscopia fetale postnatale 7%)

- Deprest et al.
"Fetal Intervention for Congenital Diaphragmatic Hernia: The Eurpean Experience" *Sem Perinat 2005*

-Deprest, De Coppi
"Antenatal management of isolated CDH today and tomorrow" *J Ped Surg 2012*

Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion

Ultrasound Obstet Gynecol 2009; **34**: 304–310

J. C. JANI†*, K. H. NICOLAIDES†, E. GRATACÓS‡, C. M. VALENCIA†, E. DONÉ*, J.-M. MARTINEZ‡, L. GUCCIARDO*, R. CRUZ‡ and J. A. DEPREST*

*Fetal Medicine and Treatment Units of *University Hospital Gasthuisberg, Leuven, Belgium, †King's College Hospital, London, UK and ‡Hospital Clinic, Barcelona, Spain*

Methods *This was a multicenter study of singleton pregnancies with CDH treated by FETO. The entry criteria for FETO were severe CDH on the basis of sonographic evidence of intrathoracic herniation of the liver and low lung area to head circumference ratio (LHR) defined as the observed to the expected normal mean for gestation (o/e LHR) equivalent to an LHR of 1 or less.*

Results *FETO was carried out in 210 cases, including 175 cases with left-sided, 34 right-sided and one with bilateral CDH. In 188 cases the CDH was isolated and in 22 there was an associated defect. FETO was performed at a median gestational age of 27.1 (range, 23.0–33.3) weeks. The first eight cases were done under general anesthesia, but subsequently either regional or local anesthesia was used. The median duration of FETO was 10 (range, 3–93) min. Successful placement of the balloon at the first procedure was achieved in 203 (96.7%) cases. Spontaneous preterm prelabor rupture of membranes (PPROM) occurred in 99 (47.1%) cases at 3–83 (median, 30) days after FETO and within 3 weeks of the procedure in 35 (16.7%) cases. Removal of the balloon was prenatal either by fetoscopy or ultrasound-guided puncture, intrapartum by ex-utero intrapartum treatment, or postnatal either by tracheoscopy or percutaneous puncture. Delivery was at 25.7–41.0 (median, 35.3) weeks and before 34 weeks in 65 (30.9%) cases. In 204 (97.1%) cases the babies were live born and 98 (48.0%) were discharged from the hospital alive. There were 10 deaths directly related to difficulties with removal of the balloon. Significant prediction of survival was provided by the o/e LHR and gestational age at delivery. On the basis of the relationship between survival and o/e LHR in expectantly managed fetuses with CDH, as reported in the antenatal CDH registry, we estimated that in fetuses with left CDH treated with FETO the survival rate increased from 24.1% to 49.1%, and in right CDH survival increased from 0% to 35.3% (P < 0.001).*

Conclusions *FETO in severe CDH is associated with a high incidence of PPROM and preterm delivery but a substantial improvement in survival.* Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.

Survival rate after FETO:

LCDH

24 → 49%

RCDH

0 → 35%

Complicanze:

-PPROM *(60%)*

-Parto pretermine *(30% < 34 SG)*

Predictors:

- O/E LHR preFETO
-SG al parto
-Rimozione balloon
> 24h prima del parto

Morbidity:

-< assisted ventilation

-< 02 needed

-< NICU stay

Doné et al

"Predictors of neonatal morbidity in fetuses with severe isolated congenital diaphragmatic hernia undergoing fetoscopic tracheal occlusion"

UOG 2013

Conclusions Fetal intervention for severe CDH is associated with neonatal morbidity that is comparable with that of an expectantly managed group with less severe disease. Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.

CDH - TOTAL TRIAL

Tracheal Occlusion To Accelerate Lung growth

"RANDOMIZED TRIAL OF FETOSCOPIC ENDOLUMINAL TRACHEAL OCCLUSION (FETO) VERSUS EXPECTANT MANAGEMENT DURING PREGNANCY IN FETUSES WITH LEFT SIDED AND ISOLATED CONGENITAL DIAPHRAGMATIC HERNIA AND MODERATE PULMONARY HYPOPLASIA".
The acronym used is 'TOTAL' (Tracheal Occlusion To Accelerate Lung growth)

www.totaltrial.eu

Who can participate?	Who can't participate?
Mother 18 years or older	Not willing to be undergoing "randomization"
Singleton pregnancy	Twins or more
Written consent	Not able to consent in full
Left sided diaphragmatic hernia	Right sided or bilateral diaphragmatic hernia
No associated anomalies and normal chromosomes	Additional problems
Gestation no more than 31 wks and 5 days at randomization	Balloon cannot be placed prior to 31 weeks and 6 days
Moderate hypoplasia defined as observed over expected lung area to head circumference 25 – 34.9 % (position of liver not relevant) OR 35 – 44.9 with liver in the chest measured at the latest at 32 weeks and 5 days	Severe hypoplasia Mild hypoplasia
Acceptance of responsibility to come to FETO center for balloon removal	Maternal diseases or technical limitations making prenatal surgery hazardous or impossible
Cervix longer than 15 mm	Short cervix (<15mm) at randomization

UZ LEUVEN

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King's College Hospital NHS
NHS Foundation Trust

universitäts klinikum bonn

CDH - TOTAL TRIAL

Tracheal Occlusion To Accelerate Lung growth

What will be measured during the study

<u>During pregnancy:</u>

- Lung growth
- Balloon position (if operated)

<u>After birth:</u>

- Oxygen dependency
- Need for medication for lung hypertension
- Need for heart-lung machine, days requiring a ventilator, until normal feeding and in the hospital
- Day of the surgery and requirement of a patch to close the defect
- Occurrence of brain problems, infections, prematurity problems, reflux

<u>Later in life patients will be called back:</u>

- Lung function at one year
- Neurologic development at one and two years

In case of non-survival the time point at which it occurs will be noted and the cause will be asked.

In non-surviving CDH babies, a so called autopsy is always recommended. Results of such examination would also be requested.

CDH – Nuove prospettive terapeutiche

1. <u>SILDENAFIL transpalcentare</u>

   per favorire vasodilatazione polmonare – rat model

Antenatal Sildenafil Treatment Attenuates Pulmonary Hypertension in Experimental Congenital Diaphragmatic Hernia

Christina Luong, BSc*; Juliana Rey-Perra, MD*; Arul Vadivel, PhD; Greg Gilmour, BSc;

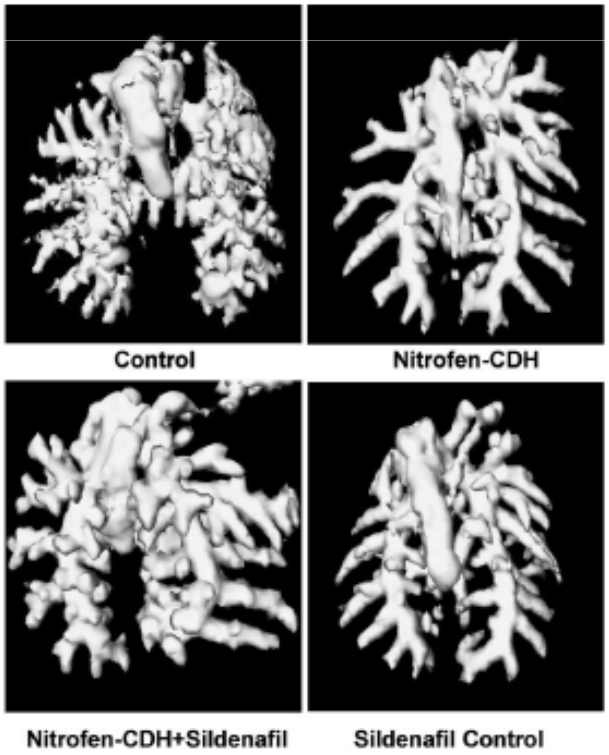
Circulation. 2011;123:2120-2131;

Antenatal sildenafil administered to the pregnant rat

In conclusion, antenatal treatment with sildenafil improves lung structure, increases vessel density, decreases RVH, and enhances dilatation to NO in experimental, nitrofen-induced CDH in rats. We speculate that the

the fetuses. Antenatal strategies may improve responsiveness to postnatal pulmonary vasodilator therapies, and ultimately the outcome of infants with CDH. The relative pulmonary vascular specificity of sildenafil, its low cost, and its postmarketing safety record makes it an attractive therapeutic option for infants with CDH.

Further clinical challenges include the choice of the timing (eg, introducing maternal sildenafil treatment early enough during gestation to positively affect the outcome), dosing, and length of treatment. Other limitations of this study



CDH – Nuove prospettive terapeutiche

2. VEGF locale intratracheale con TO

Antenatal fetal VEGF therapy to promote pulmonary maturation in a preterm rabbit model

A. Debeer [a,b,*], L. Sbragia [a], K. Vrancken [a], A. Hendriks [a], X. Roubliova [a], J. Jani [a], G. Naulaers [b], P. Carmeliet [c,d], J. Deprest [a,b]

We hypothesized that antenatal VEGF administration would stimulate type II cell differentiation, surfactant synthesis and release, which in turn would improve pulmonary mechanics.

Early Human Development 86 (2010) 99–105

Aim: To assess the effects of fetal tracheal administration of VEGF on pulmonary maturation in a preterm rabbit model.

Methods: On day 26 (term = 31 days), fetal rabbits received recombinant rat VEGF (30 µg in 70 µL normal saline) or placebo (normal saline 70 µL) intratracheally, with or without subsequent tracheal occlusion. Non-operated littermates served as internal controls. Fetuses were harvested on day 28 for morphometric study of the lungs or for mechanical ventilation and measurement of lung mechanics. In total, 96 fetuses from 42 does were used, 47 for ventilation and 49 for morphometry.

Results: In fetuses receiving intratracheal VEGF, an increase in immunoreactivity for Flk-1 was observed throughout the lung parenchyma. Tracheal occlusion (TO) adversely affected pulmonary mechanics as compared to un-occluded controls. That effect is partly reversed by intratracheal VEGF. Intratracheal injection of VEGF without tracheal occlusion improves lung mechanics but no more than what was observed in placebo injected controls.

Conclusion: Antenatal intratracheal VEGF administration was associated with an increase in Flk-1 immunoreactivity. It also improves lung mechanics, however more so when the trachea is occluded. Without TO, the effects were comparable to placebo controls.

mechanics may be put forward. The enhanced Flk-1 expression may promote type II cell differentiation and increase surfactant synthesis or release. However, further study will be required to clarify the exact mechanisms through which VEGF can improve lung maturation.

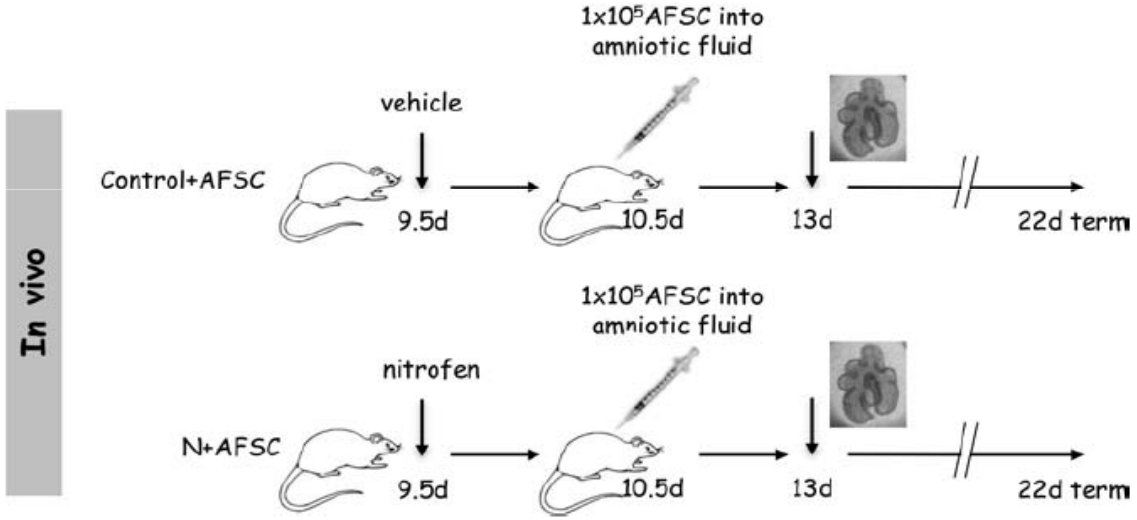
CDH – Nuove prospettive terapeutiche

3. Amniotic Fluid Derived Stem Cells

Amniotic Fluid Stem Cells Rescue Both In Vitro and In Vivo Growth, Innervation, and Motility in Nitrofen-Exposed Hypoplastic Rat Lungs Through Paracrine Effects

F. Pederiva,* M. Ghionzoli,† A. Pierro,† P. De Coppi,†[1] and J. A. Tovar*[1]

Cell Transplantation, Vol. 22, pp. 1683–1694, 2013



In vitro:
Intrapulmonary AFS
In vivo:
Intramniotic AFS

- Lung growth
- Bronchial motility
- Innervation

In the present study, we found that hypoplastic nitrofen-exposed lung explants cocultured with AFS cells were restored to the size and the number of terminal buds of the control lungs. Moreover, the frequency of peristaltic waves, which was decreased in nitrofen-exposed lungs, as expected (20), normalized after adding AFS cells to the medium. The improvement of airway peristalsis obtained

In conclusion, we have demonstrated for the first time that AFS cells can rescue nitrofen-induced hypoplastic lungs in coculture. It is possible that, as previously demonstrated in other model of disease, AFS cells might have a therapeutic role in CDH, particularly in babies with severe hypoplastic lungs. This effect could be also obtained during gestation, since AFS cells transplanted in utero in the same animal model produced a similar effect.