



TOTAL Trials et après ?

A. Benachi



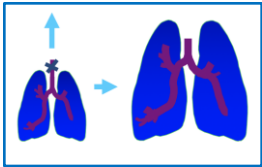
FIMATHO

Filière des maladies rares abdomino-thoraciques

Centre Maladie Rare: Hernie de Coupole Diaphragmatique

Centre Pluridisciplinaire de Diagnostic Prénatal - Paris Saclay France

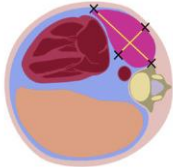
CDH and FETO a long journey



1994

Tracheal ligation

Wilson Hedrick



1996

LHR

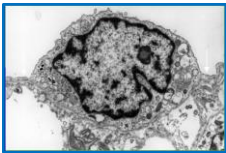
Mektus



1997

TO with ballonnet

Benachi Deprest



1998

Reversible TO

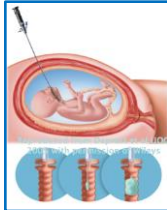
Flageole



2000

TO in human. Open

Flake



2001

FETO in human

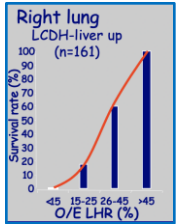
Deprest



2003

RCT TO in human

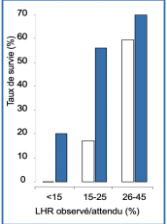
Harrison



2007

LHR o/e Standardized neonatal

Jani Euro-CDH consortium



2009

1st study on FETO

Jani



2008/2011-2019

TOTAL moderate and severe

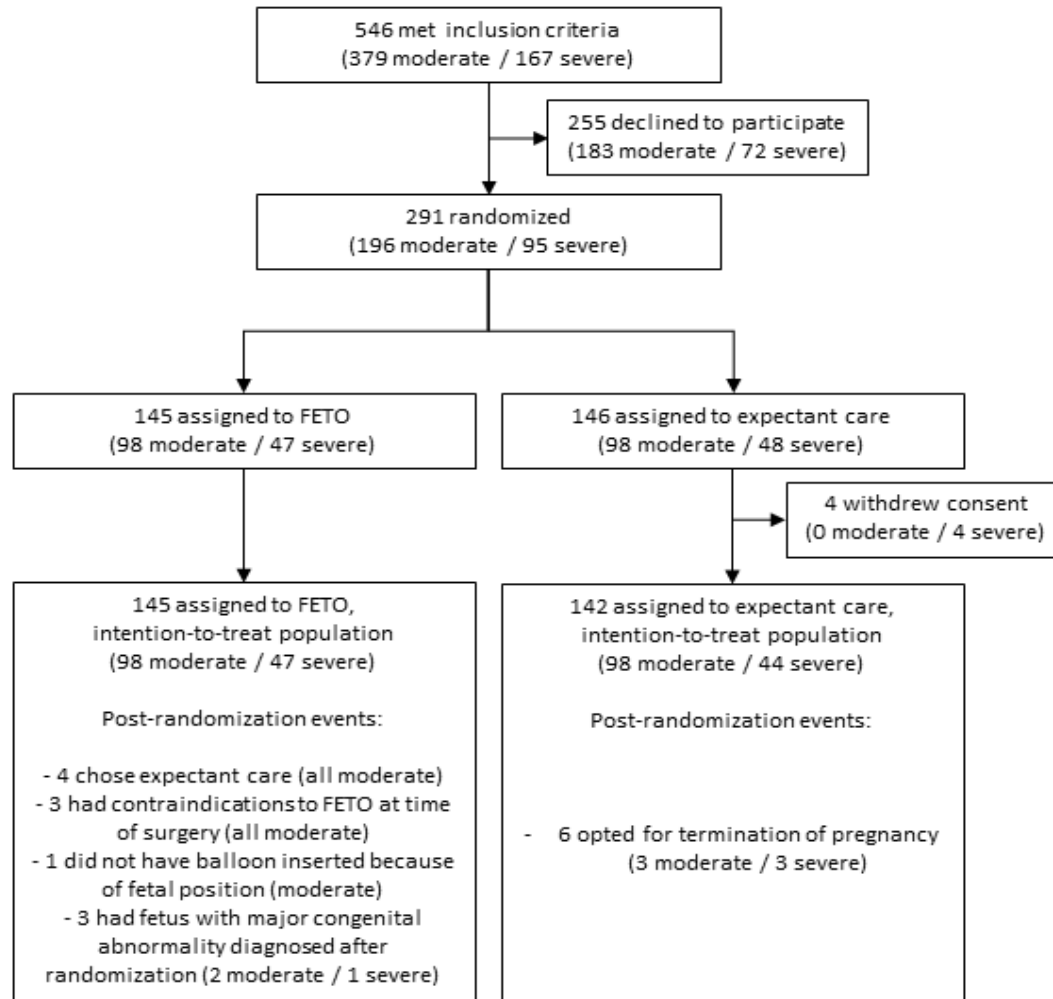
Deprest



What have we learned?

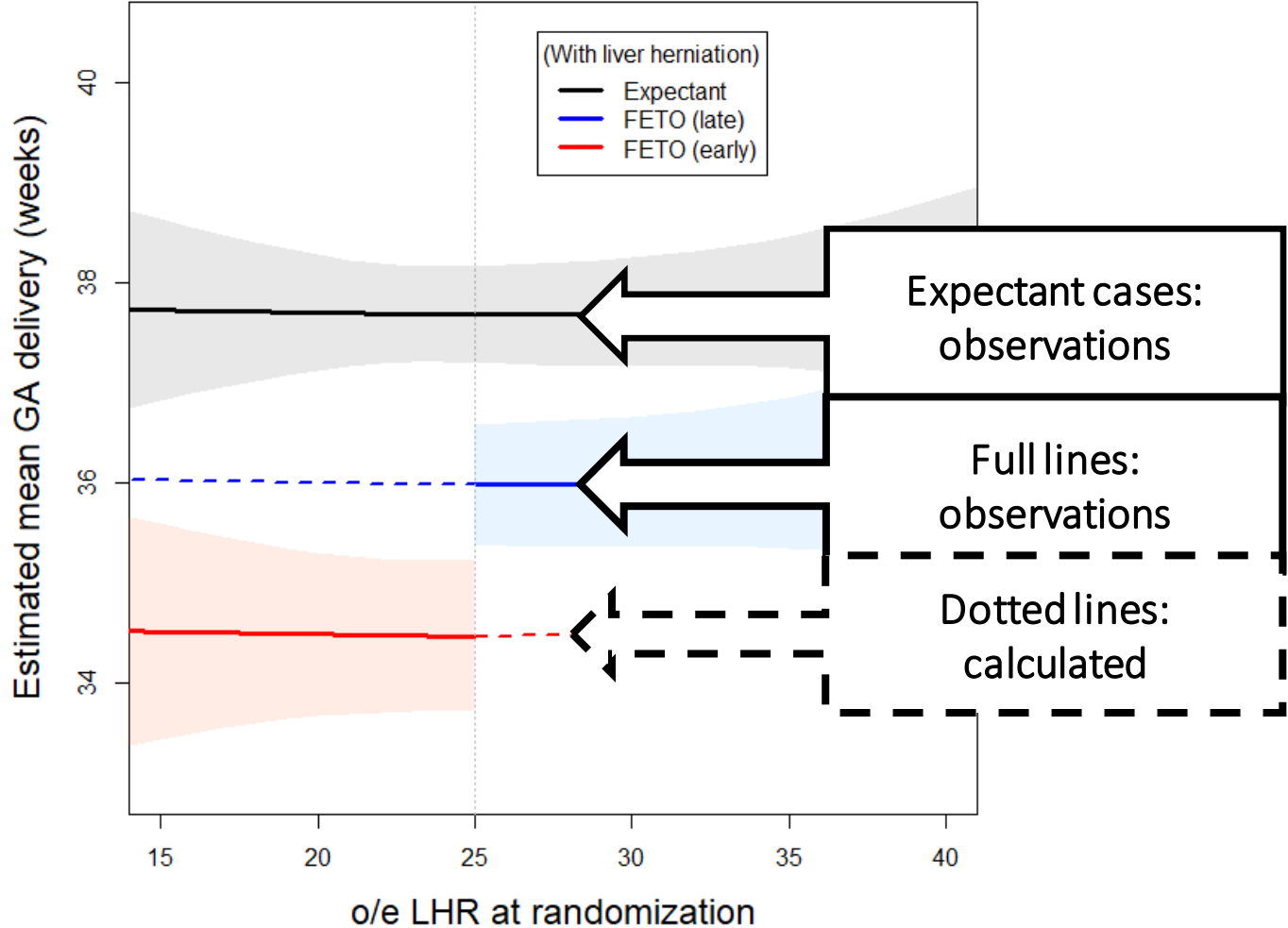
- Who is eligible for FETO?
- Maternal risks
- Fetal risks
- Patients counselling
- Team organization
- New device

Analysis pooled data

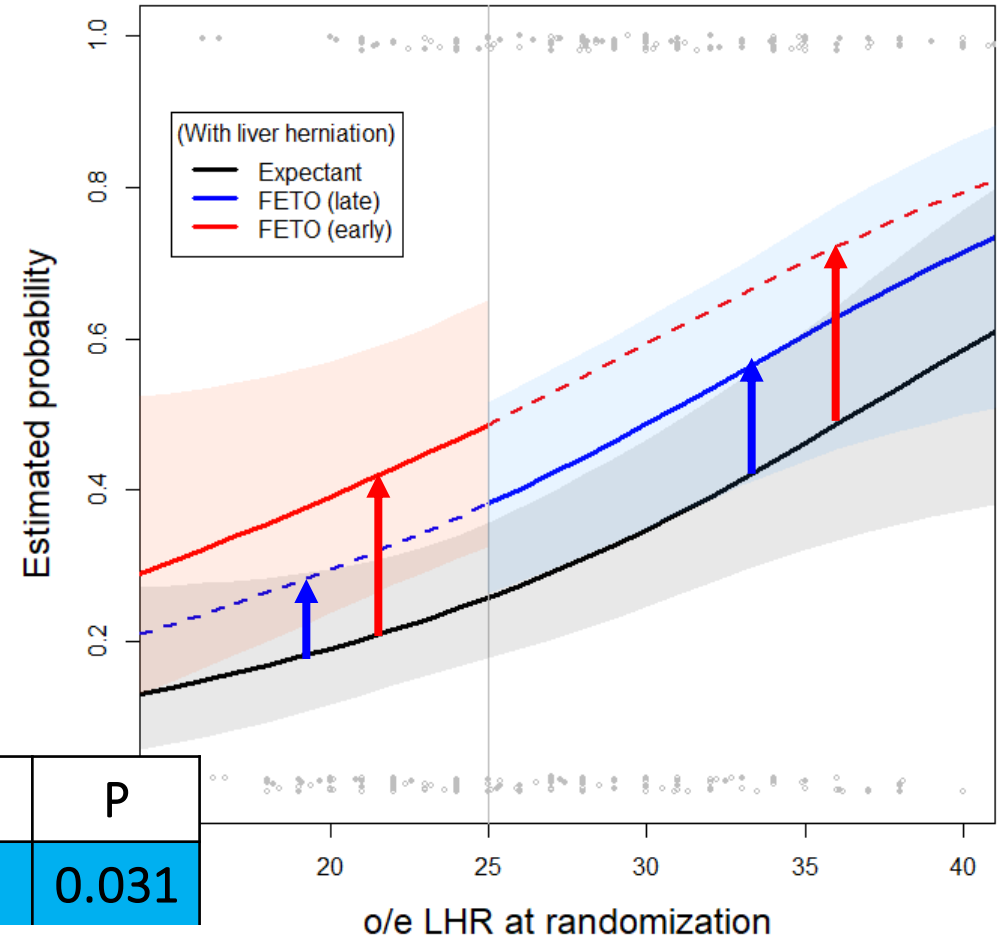
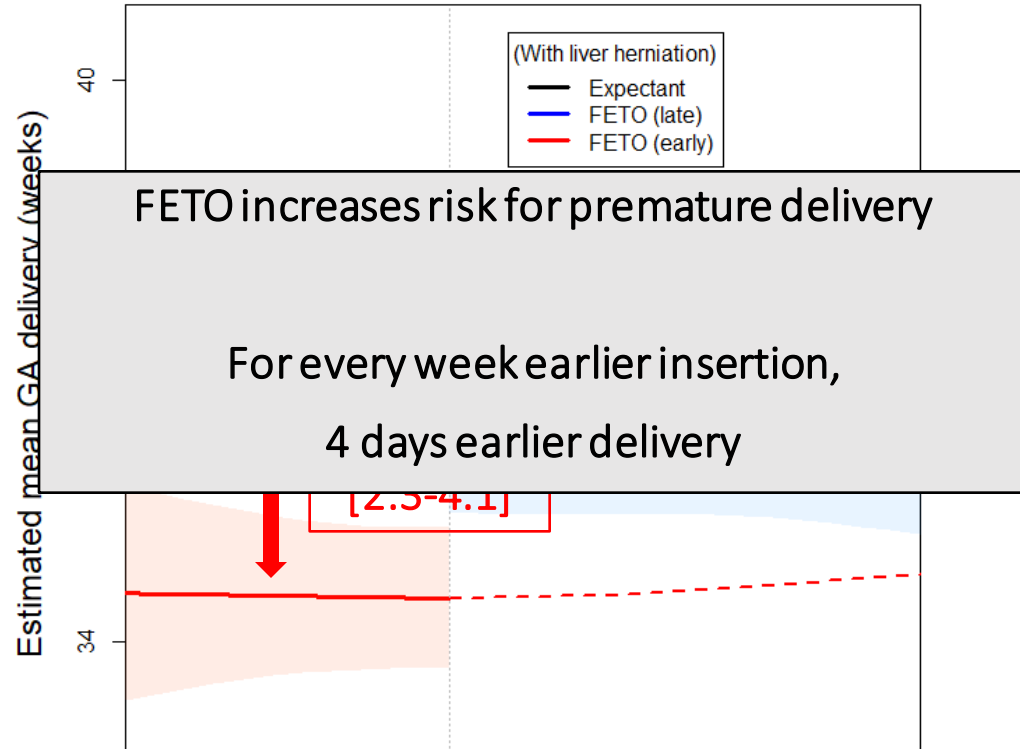


- Aim: to study heterogeneity of treatment effect by **severity (O/E LHR)** and effect of **gestational age** at tracheal occlusion.
- 291 randomized patients, consented data use
 - 196 moderate
 - 95 severe
- Method: penalized regression with covariates FETO (or not), early occlusion, o/e LHR, liver herniation, trial

Analysis pooled data



Analysis pooled data



Survival to discharge from NICU	Adjusted OR	95%- C.I.	P
Late insertion vs.expectant	1.78	1.05-3.01	0.031

Who is eligible for FETO ?

The randomized TOTAL-trials on fetal surgery for congenital diaphragmatic hernia: re-analysis using pooled data

C. What does this study add to what is already known? The discrepancy in results between the two trials is more likely due to performing FETO at an earlier gestational age in severe hypoplasia compared to moderate hypoplasia; there was no evidence that the effect of FETO depends on disease severity.

FETO can be performed between 28 et 30 WA whatever the severity
O/E LHR 25-34.9 %, liver up or down
O/E LHR 35-44.9%, liver up

CDH – Prognostic Evaluation

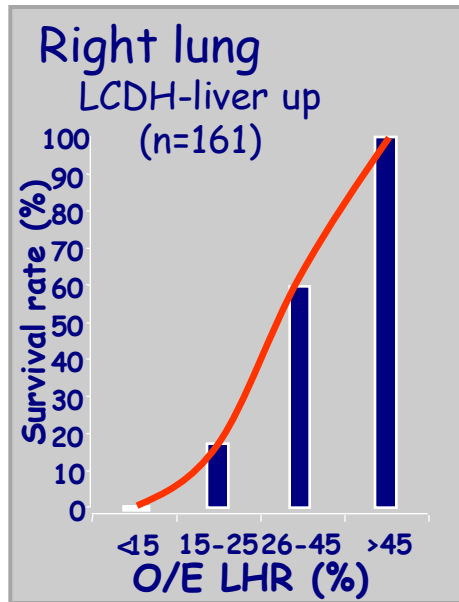
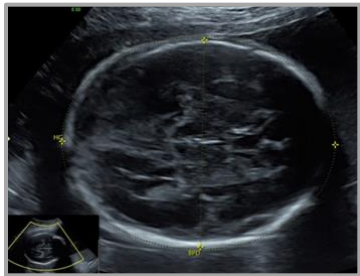
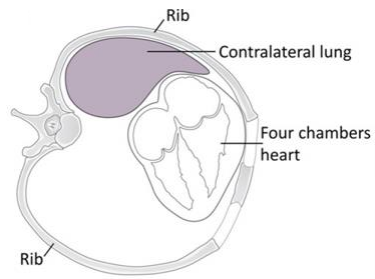
Proposal for standardized prenatal ultrasound assessment of the fetus with congenital diaphragmatic hernia by the European reference network on rare inherited and congenital anomalies (ERNICA)

Francesca Maria Russo^{1,2}  | Anne-Gael Cordier³ | Luc De Catte^{1,2} | Julien Saada⁴ |
Alexandra Benachi^{3,4}  | Jan Deprest^{1,2,5} |

on behalf of the Workstream Prenatal Management, ERNICA European reference network

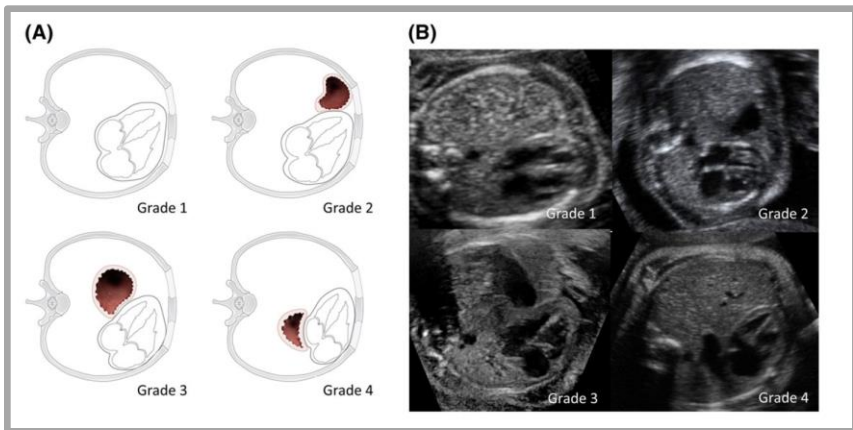
We provide a practical and instructional guide for the standardized assessment of fetuses with isolated left or right congenital diaphragmatic hernia and individualized prediction of neonatal outcome.

CDH – Prognostic Evaluation

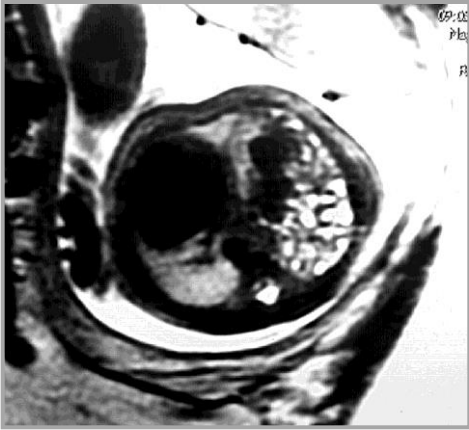


o/e LHR

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



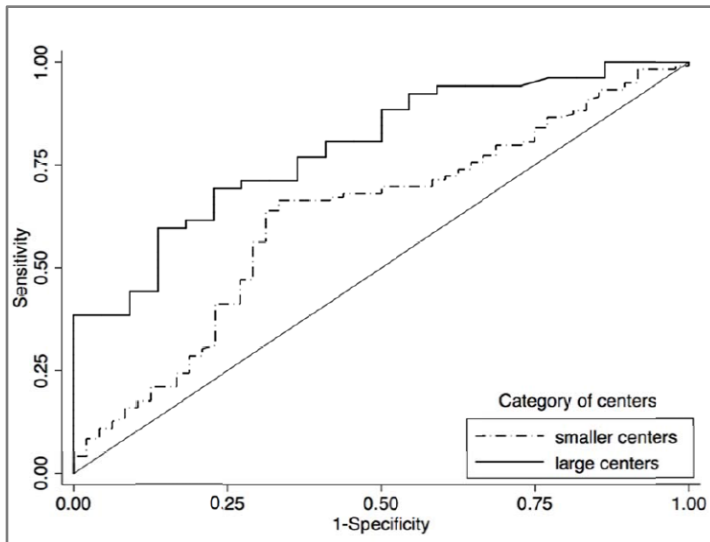
Liver position



o/e TLV MRI

Prognostic Evaluation-LHR o/e

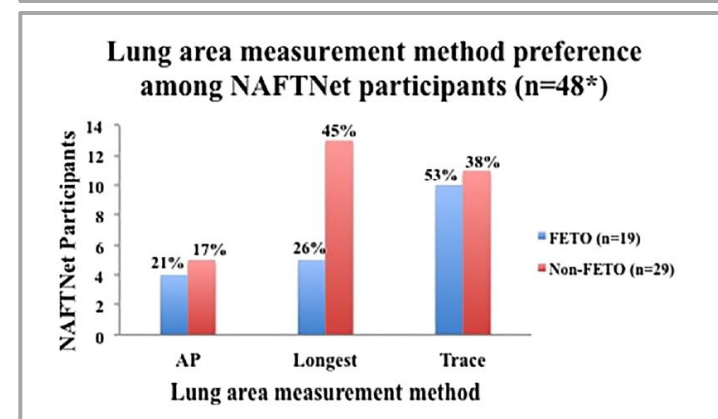
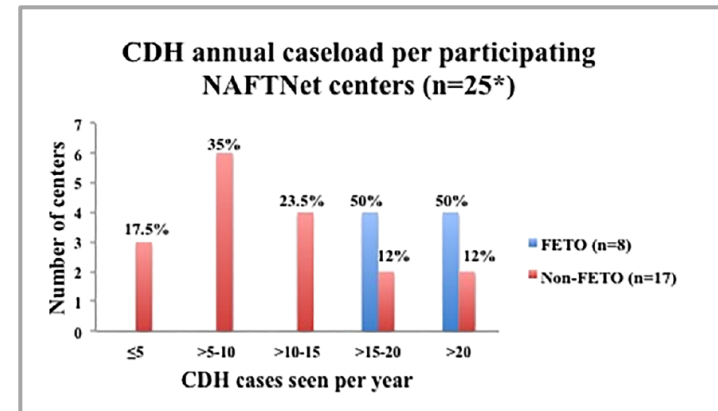
Prognosis of isolated congenital diaphragmatic hernia using lung-to-head circumference ratio: variability across centers in a national perinatal network



The overall predictive value of o/e-LHR is better when prenatal LHR measurements are performed in centers with the greatest caseload (> 14/year) and strong expertise in prenatal assessment of CDH

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*



Who is eligible for FETO ?

From the fetal side

- Not eligible
 - Polymalformation / Genetic / Chromosomal anomalies
- Should be carefully assess
 - IUGR
 - Oligoamnios/Poly-hydramnios

Who is eligible for FETO ?

From the maternal side

- Any risk of prematurity, is not eligible
 - Previous premature delivery
 - Short cervix , < 25 mm
 - Uterine malformation
 - Maternal diseases
 - Use of toxics
- Maternal infection: HIV, hepatitis B or C
- Placental position: praevia or anterior with no free window

What have we learn?

- Who is eligible for FETO?
- **Maternal risks**
- Fetal risks
- Patients counselling
- Team organization
- New device

Maternal risks

- With open surgery, up to 14% risk for uterine dehiscence and rupture
- No relevant impact of fetoscopic fetal surgery for CDH on future fertility, obstetrical and early gynecological outcomes
- 40% of patients reported a serious psychological impact of pregnancy FETO and control

Maternal risks

		Severe Complications		Minor Complications		All Complications			
Clavien-Dindo classification	IV (requiring ICU care)	III (requiring surgical intervention)	I-II (requiring treatment)	I-IV					
Open surgery n = 1193	Complication	n	Complication	n	Complication	n	ALL COMPLICATIONS: 20.86% (95% CI, 15.22-27.13)		
	Severe infection	2	Haemorrhage requiring delivery	3	Bleeding during procedure	13			
	Pulmonary oedema	4	Placental abruption	28	Transfusion during/after procedure	41			
	Complete heart block ^a	1	Bowel obstruction	1	Chorioamnionitis/endometritis	45			
			Wound drainage	2	Other infections ^b	8			
			Uterine rupture	5	Pulmonary oedema	50			
			Laparotomy/dehiscence repair	1	Transfusion at delivery	17			
			Caesarean hysterectomy	1					
	TOTAL SEVERE: 4.51% (95% CI, 3.24-5.98)		TOTAL MINOR: 16.26% (95% CI, 11.17-22.09)						
	Fetoscopic surgery n = 9403	Maternal cardiac arrest and delivery by hysterotomy	1	Sepsis requiring delivery	1	Bleeding during procedure		165	ALL COMPLICATIONS: 6.15% (95% CI, 4.93-7.49)
Severe infection		2	Haemorrhage requiring delivery	8	Transfusion during/after procedure	16			
Pulmonary oedema		3	Placental abruption	159	Venous thromboembolism ^c	2			
Lung collapse		1			Chorioamnionitis	114			
DIC + caesarean hysterectomy		1			Other infections ^d	2			
Amniotic fluid embolism		2			Pulmonary oedema	45			
					Upper GI bleed ^e	1			
					Diathermy skin burns	4			
					"Epidural headache" + blood patch	1			
					Wound hernia	1			
				Pleural effusions	1				
TOTAL SEVERE: 1.66% (95% CI, 1.19-2.20)		TOTAL MINOR: 4.33% (95% CI, 3.33-5.45)							

Meta-analysis including TTS
No control group

Placental abruption
Open: 2.34 %
FETO: 1.69%

Transfusion
Open: 3.4%
FETO: 0.17%

Maternal risks

Clavien-Dindo classification	Severe Complications		Minor Complications		All Complications		
	IV (requiring ICU care)	III (requiring surgical intervention)	I-II (requiring treatment)	I-IV			
FETO (insertion or fetoscopic removal of balloon) n = 634		Placental abruption	4	Bleeding during procedure	1	ALL COMPLICATIONS: 3.44% (95% CI, 0.98-7.32)	
				Transfusion during/after procedure	1		
				Chorioamnionitis	7		
				Wound infection	1		
				Pulmonary oedema	3		
	TOTAL SEVERE: 1.08% (95% CI, 0.23-2.54)		TOTAL MINOR: 2.39% (95% CI, 0.71-5.02)				
Fetoscopic laser photo-coagulation n = 6746	Maternal arrest and delivery	1	Haemorrhage requiring delivery	2	Bleeding during procedure	148	ALL COMPLICATIONS: 5.86% (95% CI, 4.33-7.61)
	Pulmonary oedema	3	Sepsis requiring delivery	1	Transfusion during/after procedure	9	
	Lung collapse	1	Placental abruption	130	VTE ^b	2	
	Amniotic fluid embolism	2			"Epidural headache" + blood patch	1	
	DIC + caesarean hysterectomy	1			Chorioamnionitis	68	
					Pulmonary oedema	11	
					Upper GI bleed ^c	1	
				Wound hernia	1		
	TOTAL SEVERE: 1.51% (95% CI, 0.91-2.25)		TOTAL MINOR: 4.03% (95% CI, 2.73-5.56)				

Safety data from TOTAL Trials*

	FETO n=40	Expectant n=38 [^]	FETO n=91 [°]	Expectant n=95 [§]
Bleeding at trocar insertion	1 (2%)	NA	5 (5%)	NA
Placental abruption	1 (2%)	1 (3%)	0 (0%)	0 (0%)
Chorioamnionitis	0 (0%)	1 (3%)	1 (1%)	1 (1%)
Vaginal bleeding			3 (3%)	0 (0%)
Placental laceration during removal	1 (2%)	NA		
Polyhydramnios at follow up	12/35 (34%)	NE	22/88 (25%)	

[^]2 TOP

[°]98 participants minus 7 participants did not have a surgical procedure: 4 participants decided not to undergo FETO, and the other 3 did not undergo FETO (ruptured membranes (1), a very short cervix (1), and poor fetal position (1))
[§] 98 minus 3 TOP

*The safety population included all the participants who underwent randomization and who effectively received their assigned prenatal treatment

What have we learn?

- Who is eligible for FETO?
- Maternal risks
- **Fetal risks**
- Patients counselling
- Team organization
- New device

Safety data from TOTAL Trials*

	FETO n=40	Expectant n=38 [^]	FETO n=91 ^o	Expectant n=95 [§]
Fetal death during pregnancy	0	0	1 (1%)	1 (1%)
Neonatal death due to removal failure	1 (2%)	NA	2 (2%)	NA
Tracheomalacia or tracheal damage	1 (2%)	0 (0%)	2 (2%)	NA
Chorioamniotic membrane separation	8/37 (22%)	NE		
PPROM < 37SA	19 (48%)	4 (11%)	42 (46%)	11 (12%)
Delivery < 37 SA	30 (75%)	11 (29%)	60 (66%)	22 (23%)
Bilateral hydrothorax			1 (1%)	0 (0%)

*The safety population included all the participants who underwent randomization and who effectively received their assigned prenatal treatment

Technique and safety

- Insertion failure
 - Fetal position
 - Placenta localisation
- Spontaneous balloon deflation
 - Off label use of a device meant for vascular occlusion
 - 6% (8/130), id to literature (*Jimenez et al. AJGO 2017*)
- Removal problems
 - 3/130: Failure to retrieve, wrong obstetric unit , lengthy removal

Balloon retrieval	N	Foetoscopy	Intra-uterine puncture	Post-natal
Emergency	38%	59%	12%	20%
Planned	59%	97%	3%	0%
		82%	7%	11%

Balloon removal

Intra-uterine puncture



Foetoscopy



Balloon removal

Post-natal



TEAM ORGANISATION 24/7



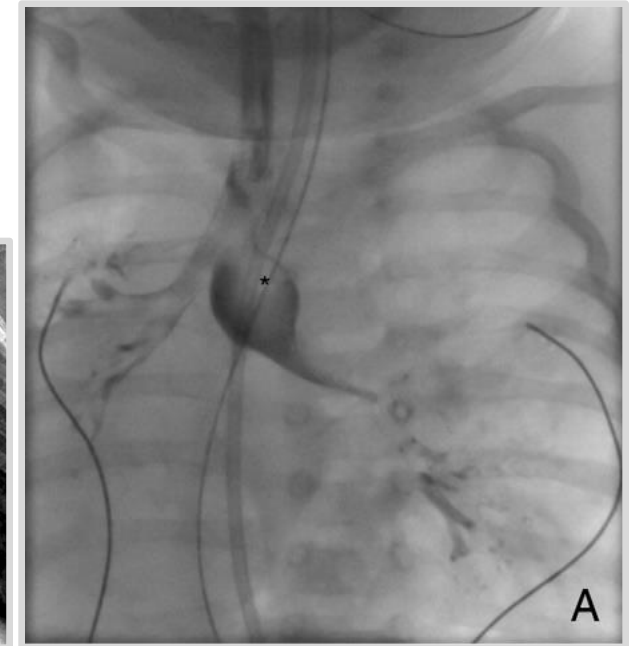
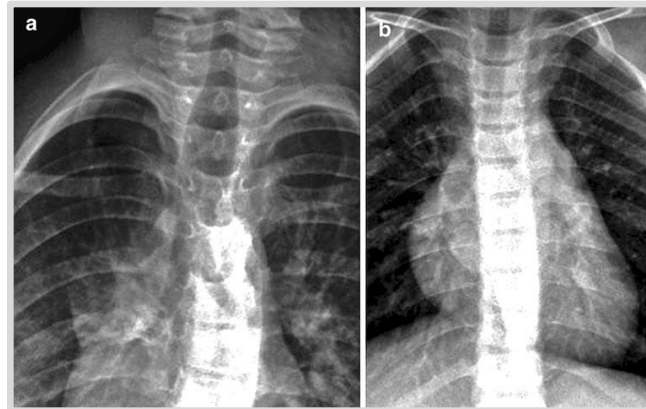
Tracheal and bronchial damage

- Tracheomegaly

- Rare and Exceptional after 28 weeks
- Tracheal dilatation without respiratory symptoms
- \neq GERD
- Normalize at 5 years

- Bronchomegaly

- Right CDH



	Panel A	Panel B	Panel C
Pars membranacea at the level of normal trachea			
Pars membranacea at the level of tracheomegaly			
Staining	hematoxylin and eosin	Elastic - Van Gieson	Myosin immunostaining

Left bronchus in right CDH

Fayoux P et al. J Ped Surg 2010
 Speggorin S et al. J Ped Surg 2011
 Goya e et al. Pediatr Radiol 2012

Genetic anomalies

Diagnosis	Timing	Group	Analyse ITT
Tetrasomy 12p	Prenatal	FETO	No
Large cardiac ventricular septum defect	Postnatal	FETO	Yes
Golz Syndrome	Postnatal	Expectant	Yes
Mutation filamin A gene	Postnatal	FETO	No
Mosaic trisomy 2	Postnatal	FETO	Yes
Duplication chromosome 8	Postnatal	FETO	Yes
Goldenhar	Postnatal	FETO	Yes
Simpson Golabi Behmel	Postnatal	FETO	No
Hypoplastic left heart syndrome	Postnatal	FETO	Yes
Tetrasomy 12p	Prenatal	Expectant	No
Tetrasomy 12p	Postnatal*	Expectant	Yes*
Fryns syndrome	Postnatal	Expectant	No

Postnatal diagnosis : diagnosis prior to discharge from NICU except in *

What have we learn?

- Who is eligible for FETO?
- Maternal risks
- Fetal risks
- Patients counselling
- Team organization
- New device

Patient counselling

- Needs for proper counselling
 - Diagnosis of CDH
 - Isolated CDH
 - Proper evaluation of LHR o/e and Liver location
- Among fetal surgery referrals over 2 years (n=86 including 12 right CDH)
 - 2% did not have CDH
 - 10% undiagnosed associated anomalies
 - Discordance: 7% for liver position; 33% for lung size
 - 72% patients referred for FETO met the inclusion criteria
- Deal with the discrepancies

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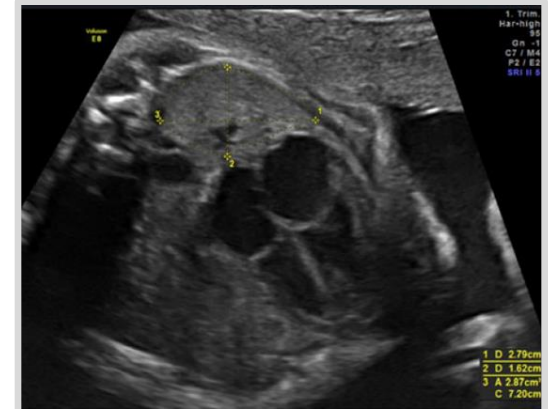
Balloon insertion

- Perfect position, avoid transverse
- Often need fetal manipulation
- Amnio-drainage/infusion
- Never cross the placenta
- Fetal anesthesia, intra-funicular or muscular
- Balloon location



Team organization

- Tele-consultation with the parents
- If eligible and agree for FETO transfer to FETO center
- Stay for 6 weeks close to hospital
- 24/7 on call for FETO team
- Back to original center after balloon retrieval



Team training

- ENT
- NICU training every 6 months
- What to do in case of obstetrical emergency?



What is next?

- Who is eligible for FETO?
- Maternal risks
- Fetal risks
- Patients counselling
- Team organization
- New device

- SMART-TO (NLS) (U.D. / A.D. / L.I.)
 - First patient
 - No radiation
 - Modern
 - Same cost



Conclusion

- Increase early prognosis with FETO
- Long term follow-up

- Induce prematurity
- Risk of increase the chance of survival of a severely sick child
- Parallel improvement of post-natal care

- How many centers/countries?
- Access to care everywhere in the country but expertise in assessment and fetoscopy needed

Centre de Référence Maladie Rare Hernie de Coupole Diaphragmatique

