



Level I evidence for fetal surgery

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Conditions eligible for fetal surgery (evidence based)

- Certain diagnosis
- Predictable natural history
- Treatment cannot wait
- Experimental basis therapy required
- Offered within trial, multidisciplinary team

International Fetal Medicine
and Surgery Society - 1991



old news

Monochorionic twins
Twin-Twin Transfusion Sd

Eurofoetus

Senat, Deprest & Ville, NEJM 2004

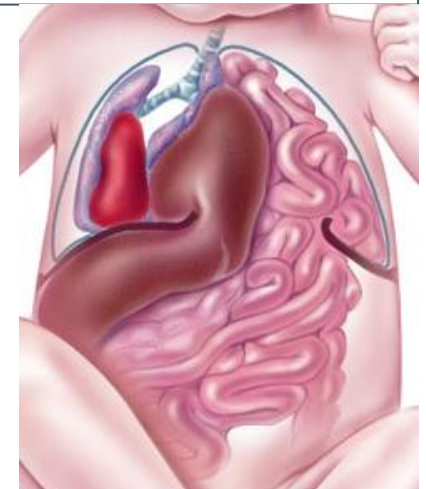


news to come

Open spina bifida

MOMS

Adzick, NEJM 2011



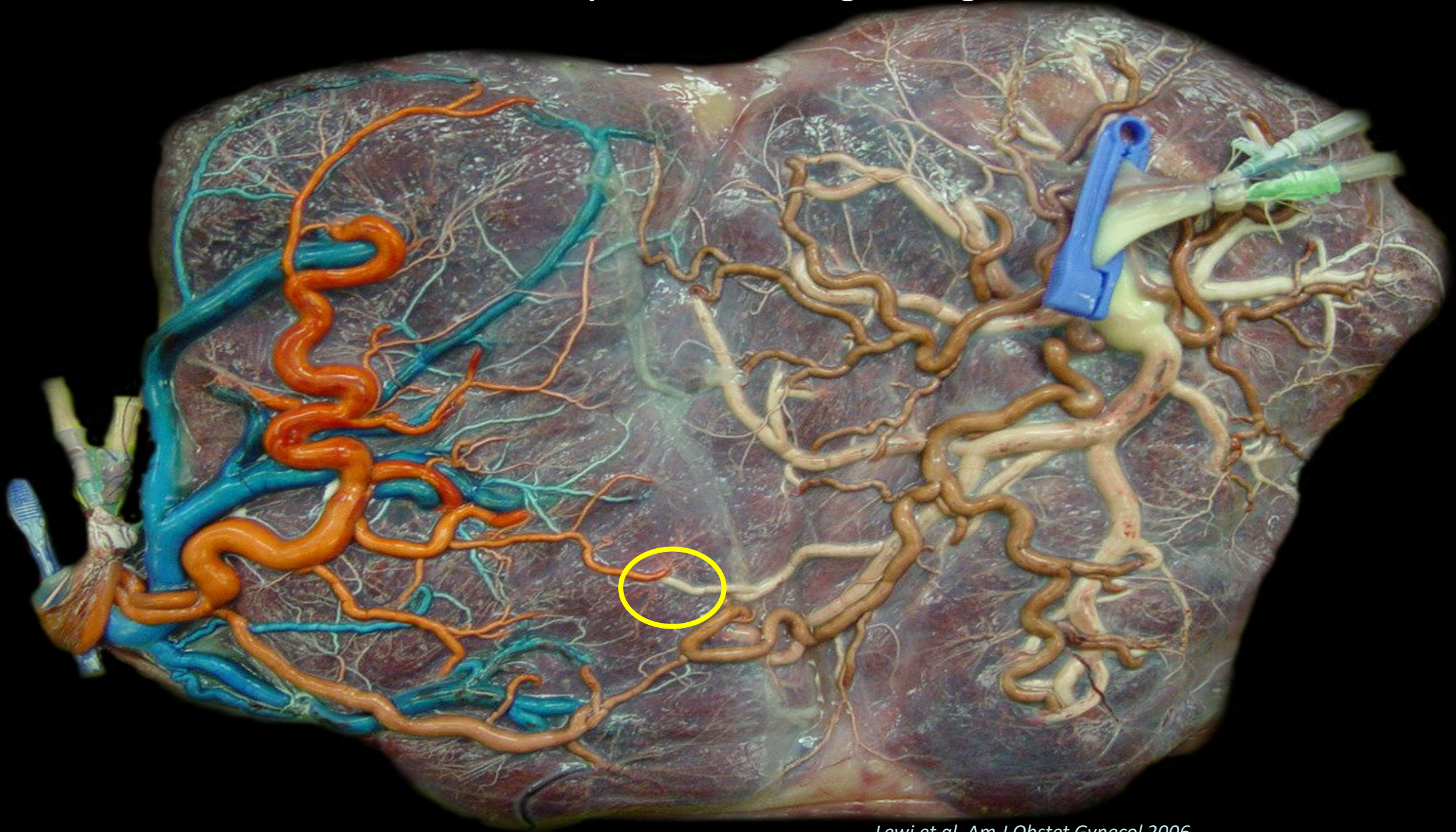
recent news

Congenital diaphragmatic hernia

TOTAL

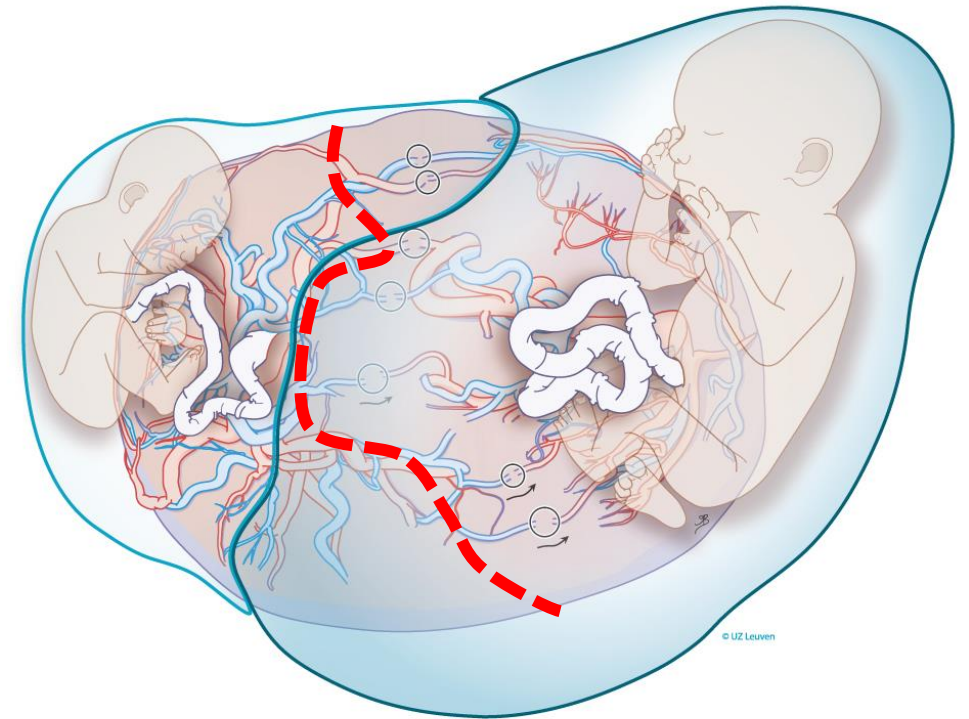
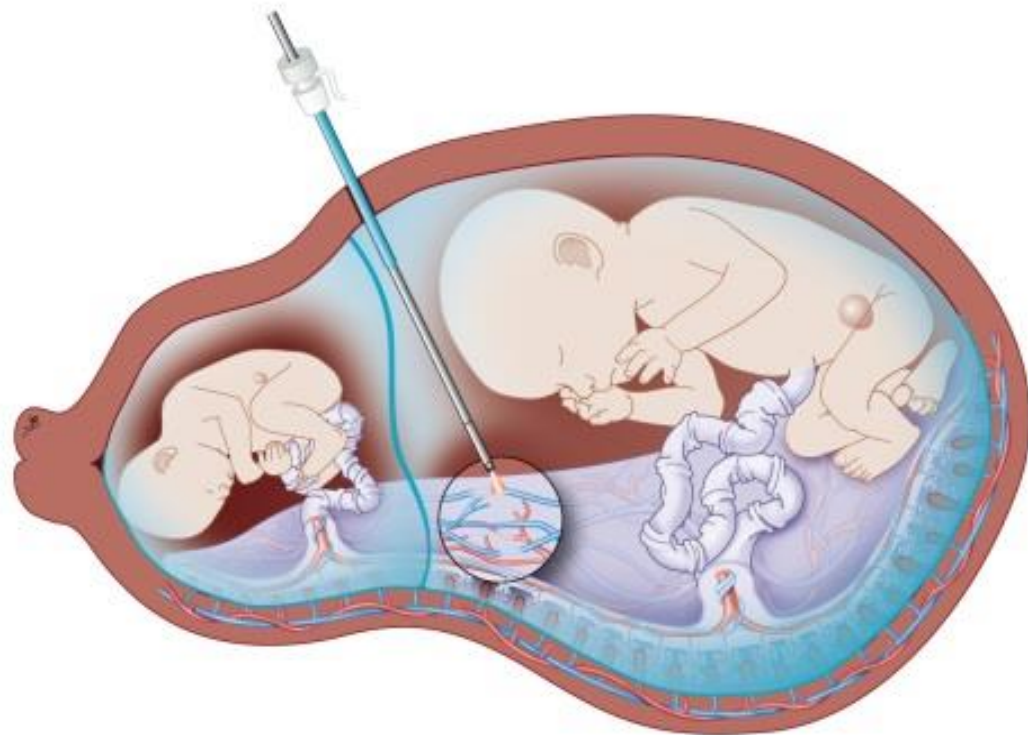
Deprest, NEJM 2021

The “siamese” placenta as a surgical target





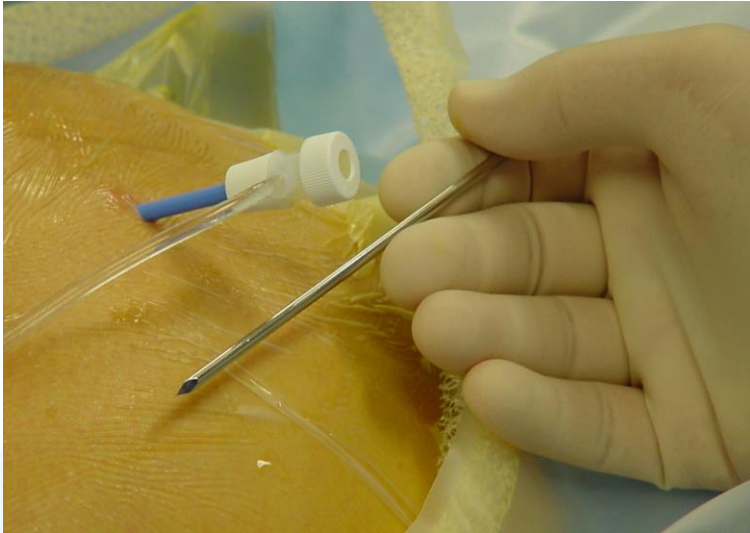
TTTS/TOPS: Twin Oligouria Polyhydramnios Syndrome



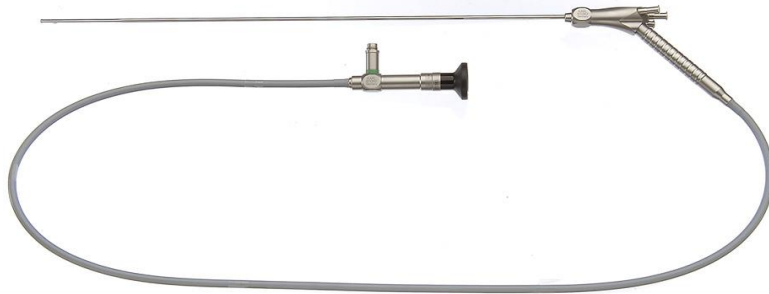
Creating two independent vascular territories



Twin to Twin Transfusion Syndrome



Percutaneous ambulatory procedure
Maternal **local** anesthesia
3.0 mm cannula diameter
No fetal medication



Fiber endoscopes & ultrasound guidance
1.2 – 2.0 mm
< 1.0 mm working channel





The Eurofoetus trial



Endoscopic Laser Surgery versus Serial Amnioreduction for Severe Twin-to-Twin Transfusion Syndrome

Marie-Victoire Senat, M.D., Jan Deprest, M.D., Ph.D., Michel Boulvain, M.D., Ph.D.,
Alain Paupe, M.D., Norbert Winer, M.D., and Yves Ville, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

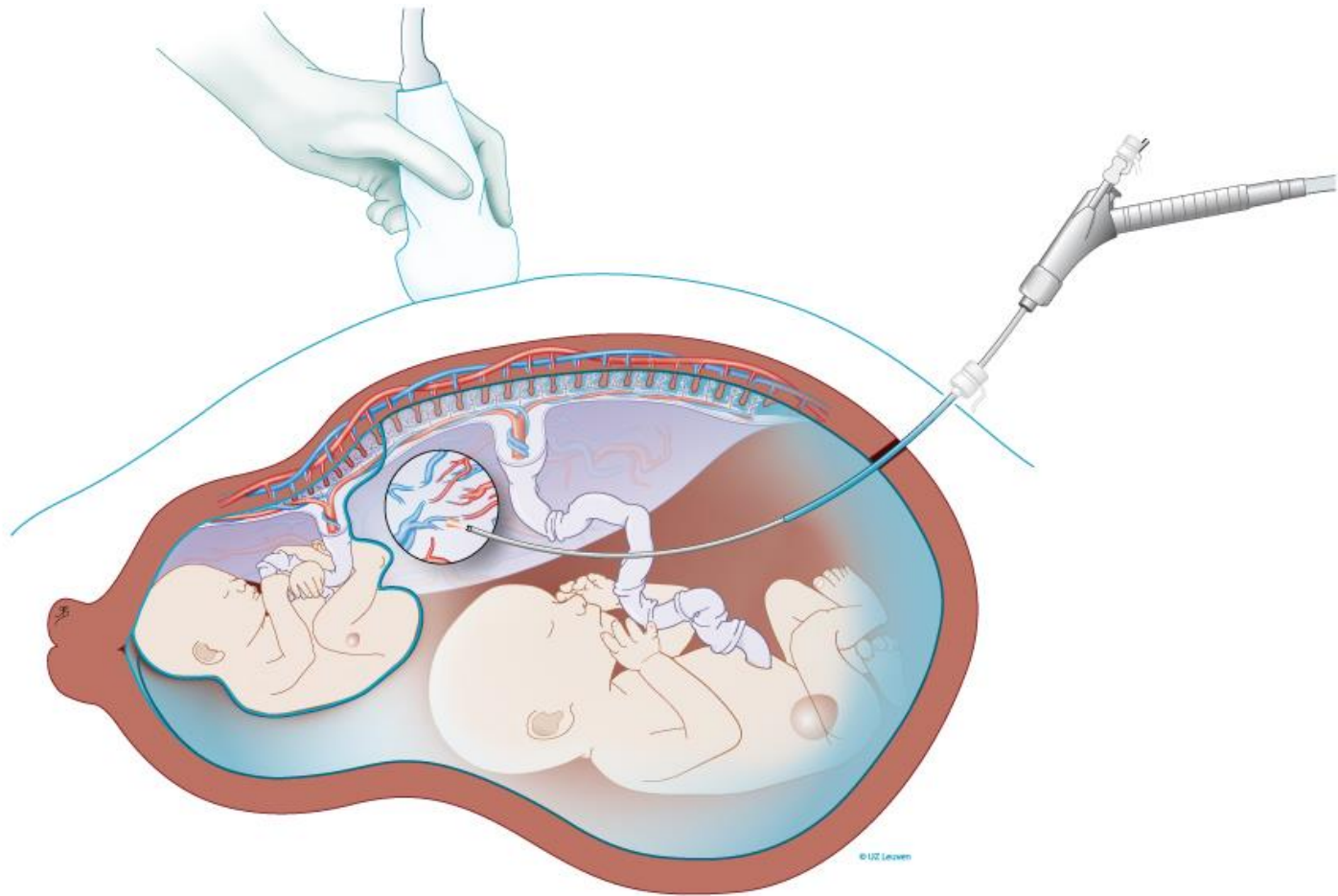


	Laser	Drainage	p
1+ surviving	76%	51%	0.002
0 survivors	24%	49%	0.02
1 survivors	46%	26%	0.002
2 survivors	36%	26%	
GA at delivery	33.3	29	0.004
neuro @ 6 mo	4.5%	10%	0.03
neuro @ 5 yrs	10%	15%	0.04

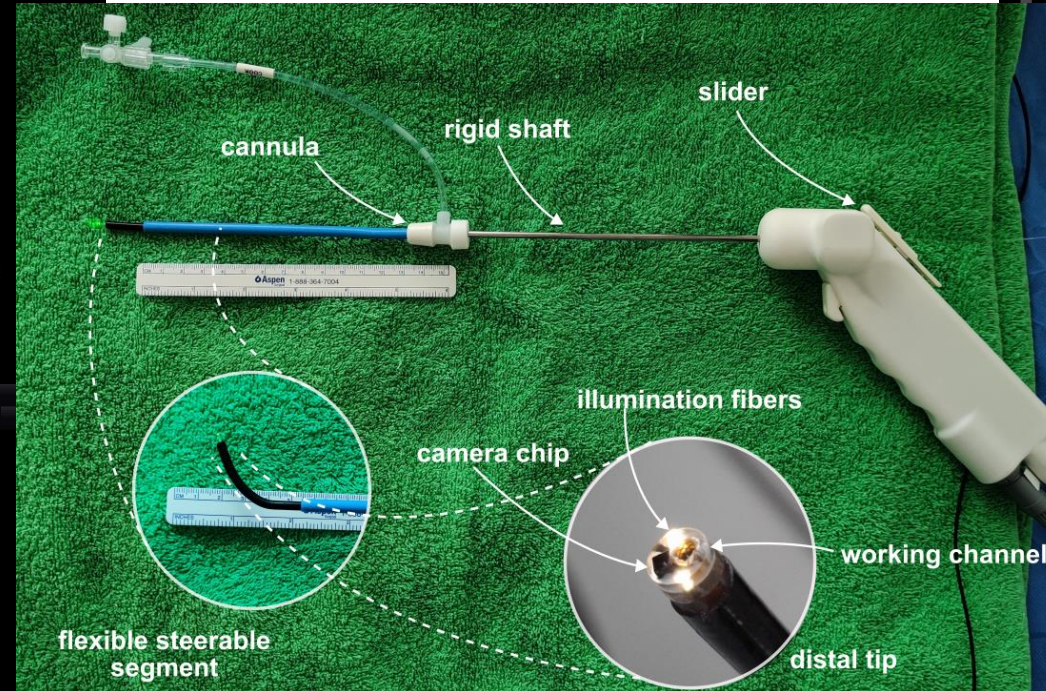


*De Lia, 1990; Ville, 1995
Salomon, et al – AJOG 2010*

Anterior placenta



Prototype flexible endoscopes



11 French

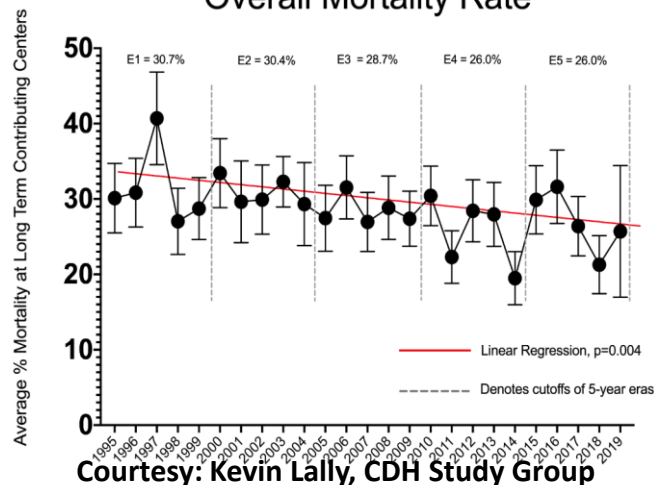
Ahmad, Van der Poorten, Deprest:
J Comp Ass Radiology Surgery 2023

Congenital Diaphragmatic Hernia

Video A Youssef



Overall Mortality Rate

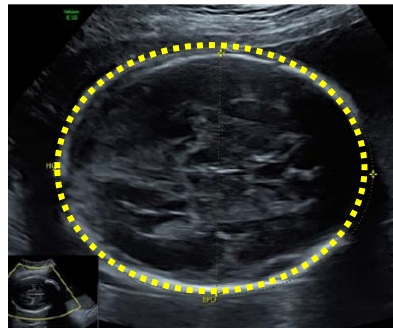
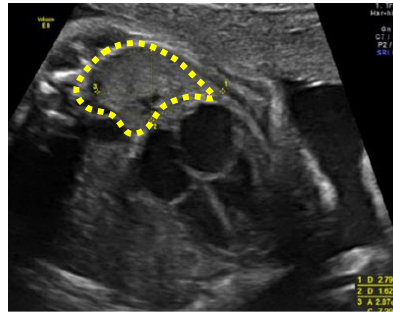


Courtesy: Kevin Lally, CDH Study Group

- 1/ 4000 births (ORPHA: 2140)
 - Side:
 - Left: 85%, right: 13%
 - Non isolated : >30% (*Russo, PND 2018*)
 - Surgically correctable but functional problem (*Zani, Nature Rev Dis Primers, 2022*)
 - Ventilatory Insufficiency
 - Pulmonary Hypertension
 - Ventricular Dysfunction
 - Feeding problems
 - Long term morbidities
- } Trifecta
- Up to 30% mortality
 - If prenatal diagnosis: 2/3 cases (*Gallot, UOG 2007; Syngelaki, UOG 2019*)
 - When one can define future non-survivors at birth
 - Can we operate before birth to improve prognosis ?

Define non survivors: prenatal severity assessment

LUNG



Lung to Head Ratio
Metkus 1996

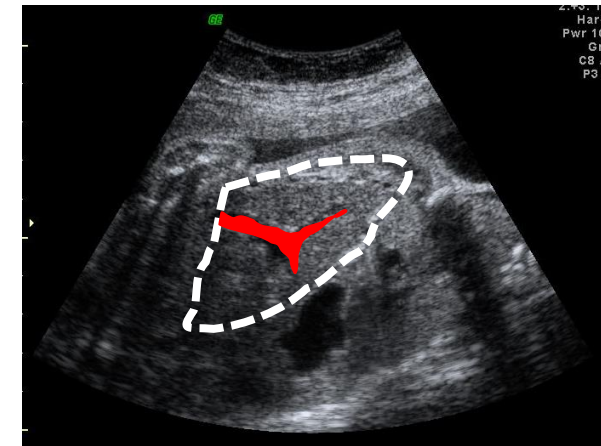
Correction for gestational age
"Observed/Expected LHR"
Peralta et al 2005
Jani et al 2007



Standardized assessment
Russo, Prenat Diagn 2018



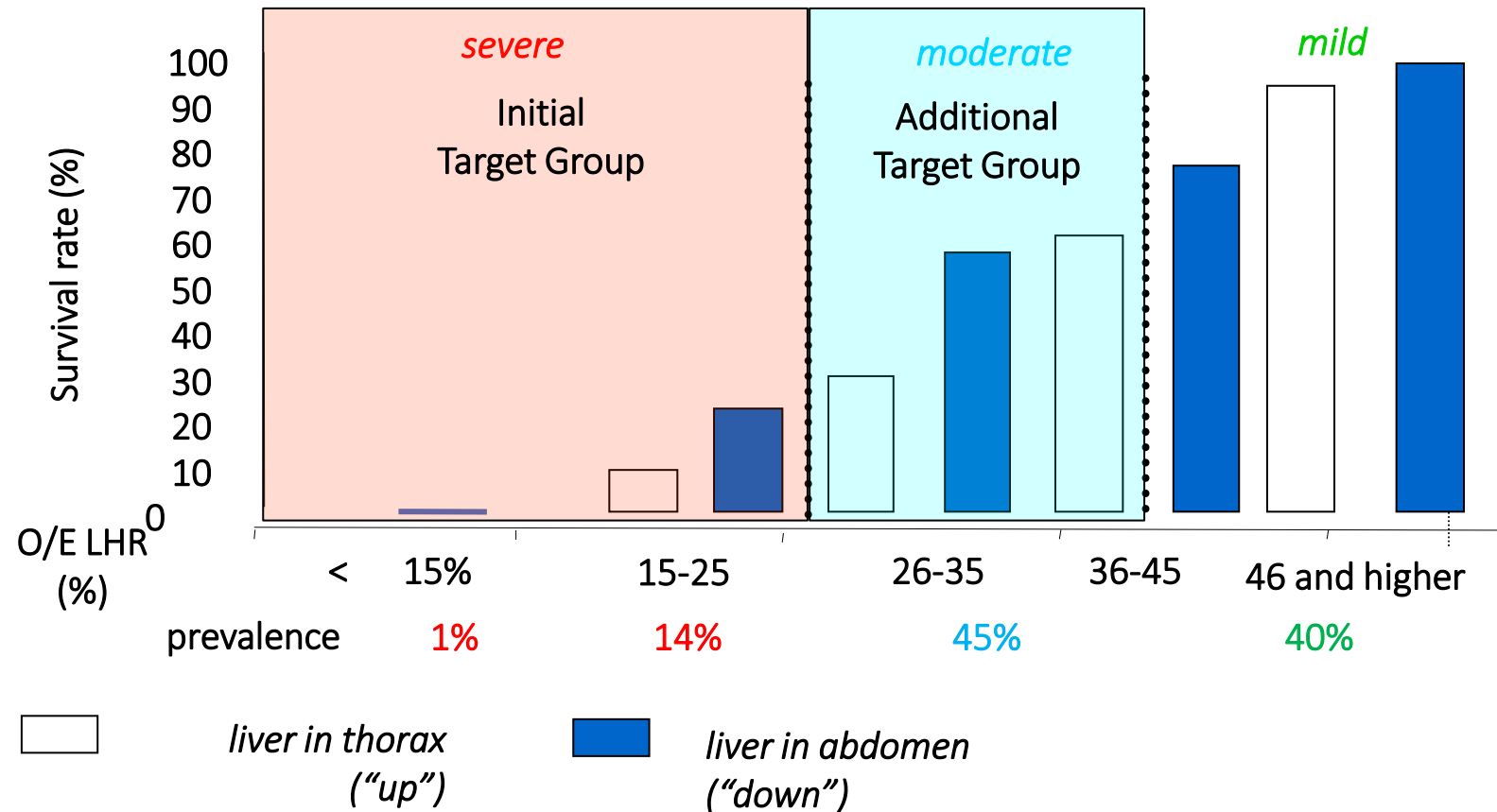
LIVER



Liver herniation

Antenatal CDH registry 2006
Mullasery UOG 2010

Defining the target population

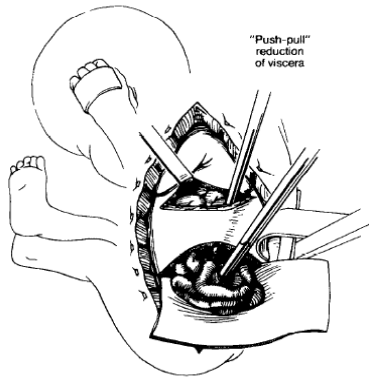


Antenatal Registry – Jani et al, UOG 2008

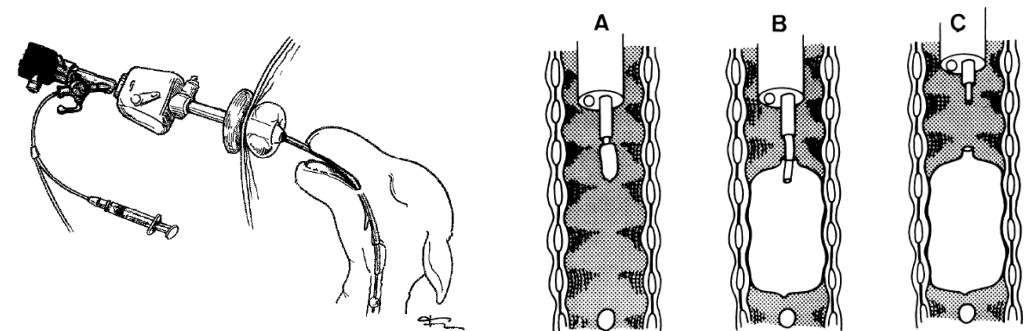
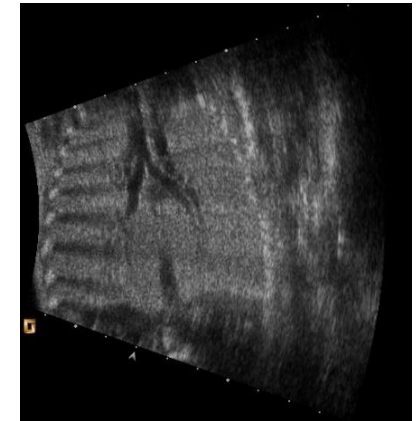
(n=329 LCDH) -Depreest J et al, Sem Neonat Fetal Med, 2008; DeKoninck, Early Human Devpt 2011.



Anatomical repair : creation of space - *Harrison J Ped Surg 1992: 2-step dance of necessity*



Tracheal occlusion
Carmel, 1965; Wilson, 1993



Pathophysiology and surgical technique
(Depreest 1995, Evrard, 1996, Flageole, 1998)

Experimental basis of fetal **tracheal occlusion**

Certain diagnosis

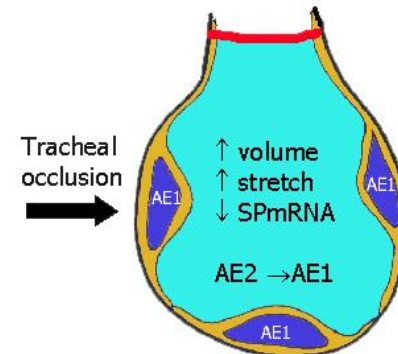
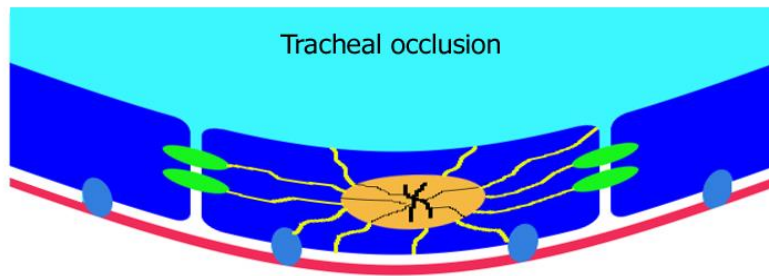
Predictable natural history

Treatment cannot wait

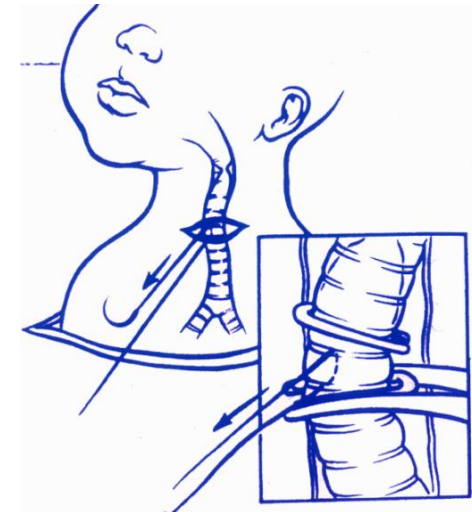
Experimental basis therapy required

Should be offered within clinical trials by multidisciplinary experts

International Fetal Medicine and Surgery Society - 1991



Proliferation, but :
 abnormal differentiation ↓AE2, ↓ surfactant, change in Na/Cl
(Evrard Ann Surg 1996; Flageole 1997, Deprest 1998)



Flake et al, 2000

Experimental basis fetal **temporary** tracheal occlusion

Certain diagnosis

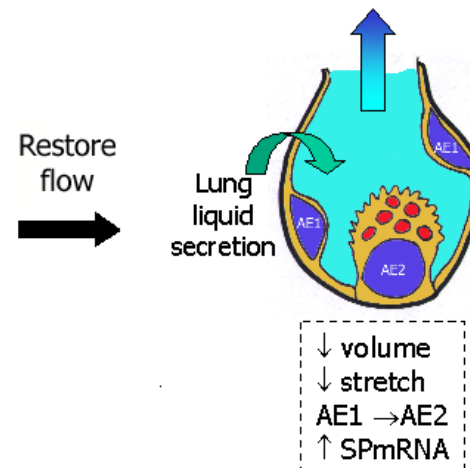
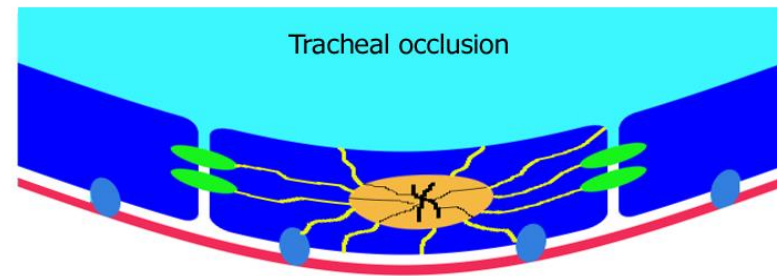
Predictable natural history

Treatment cannot wait

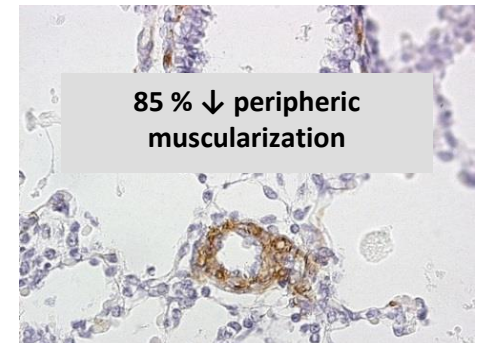
Experimental basis therapy required

Should be offered within clinical trials by multidisciplinary experts

International Fetal Medicine and Surgery Society - 1991



Induction of maturation, reverses muscularization, improved function
Flageole, JPS 1997, Roubliova, JPS 2004, AJOG 2004

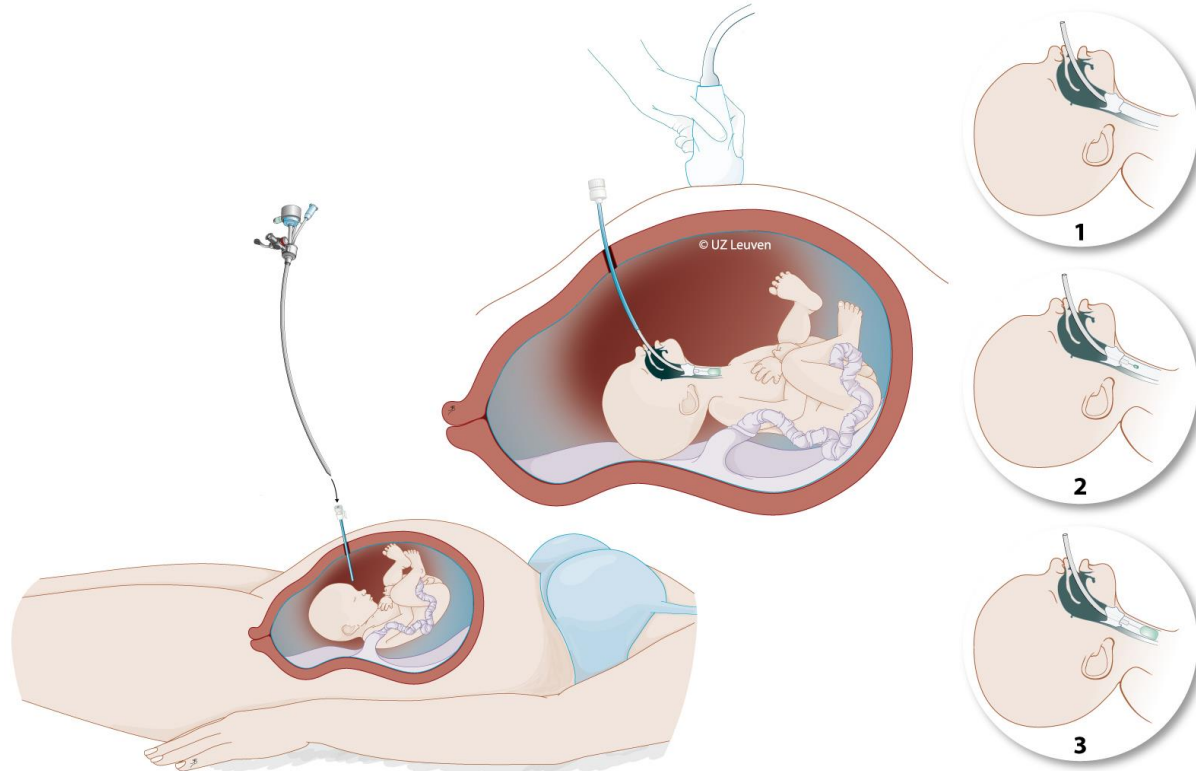


Fetal endoscopic tracheal occlusion (FETO)

2004: First-in-woman – insertion of balloon @ 26-27 wks

Maternal local anesthesia – 3.0 mm incision

Fetal systemic anesthesia: fentanyl + curare



Depreest, UOG 2004



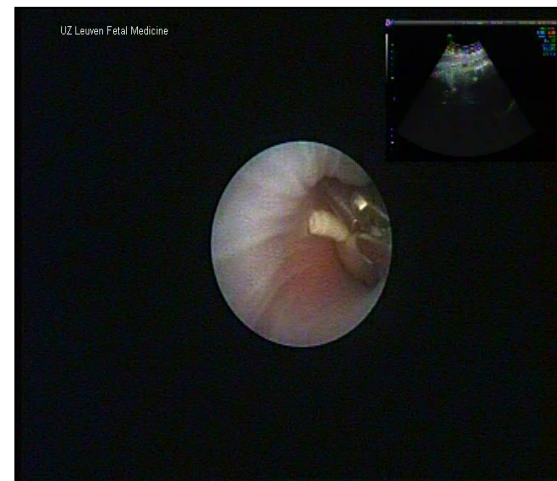
Re-establishment of the airways @ 34 weeks

PLUG-Unplug sequence:
reversal occlusion inducing lung maturation
Flageole, J Ped Surg 1998

Ultrasound Guided Puncture



Fetoscopic Retrieval



Removal during c section





Clinical trial FETO



Indications: severe pulmonary hypoplasia
(predicted survival chances $\ll 20\%$)

Survival increase

$<20\% \rightarrow 50\%$ for left sided CDH (n=175)

Predictors survival

- *gestation at delivery* ($p < 0.001$)
- *balloon removal >24 hrs* ($p < 0.001$)

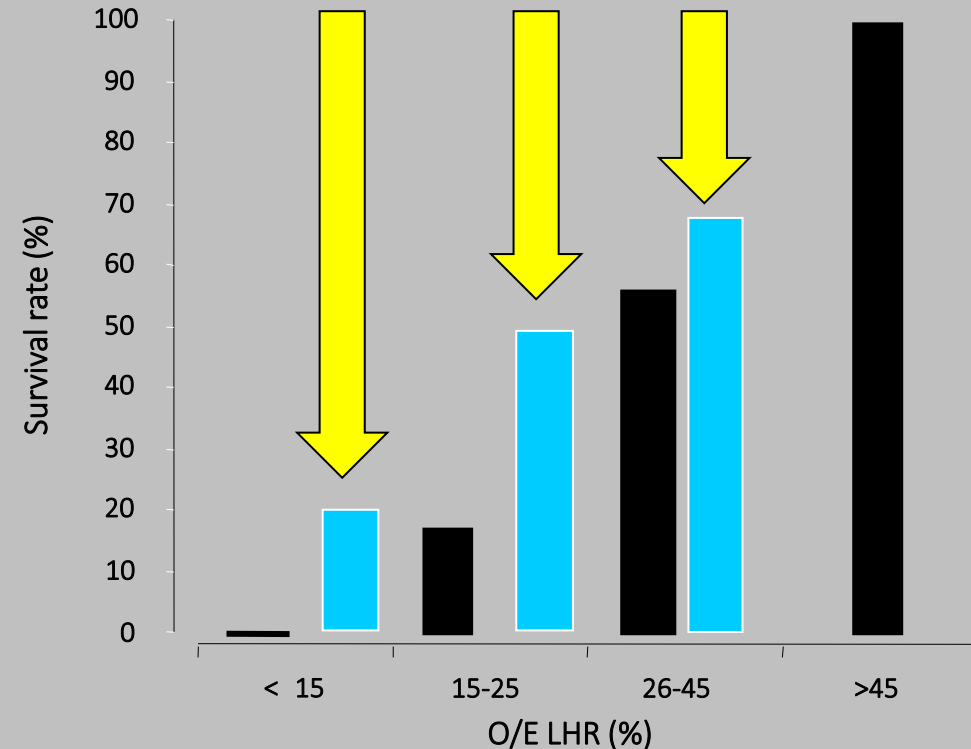
Peralta, AJOG 2007 – Jani, UOG 2009 – Sinha JPS 2009 - Done 2011, 2013 – Ali JPS 2013

Increases **prematurity**

- Membrane rupture: RR: 1.7 (0.8-2.4)
- Preterm birth: RR: 1.8 (0.8-3.9)

Done UOG 2013

Right (contralateral) lung



FETO Consortium, UOG 2009

n=210 consecutive cases

Positive proof of global warming.



**18th
Century**

1900

1950

1970

1980

1990

2006



Tracheal Occlusion To Accelerate Lung growth



- Two open-label, randomized 1:1, multicentre, superiority trials
- *Primary outcome: survival to discharge from NICU*
- Group sequential design, 5 interim analyses, ITT, $\alpha=0.05$; $\beta=0.8$

Severity	Hypothesis	Sample size
Severe	Increase 25 → 50%	2*58
Moderate	+ 20 % increase	2*98

Time point of occlusion		
Severe	Early occlusion	27-29 weeks
Moderate	Late occlusion	30-31 weeks
Time point removal	“unplug”	34 weeks



TOTAL trial : results



	Severe CDH		
Primary outcome	FETO N=40	Expectant N=40	RR / Diff (95% CI)
Survival at discharge	40%	15%	2.67 (1.22-6.11)



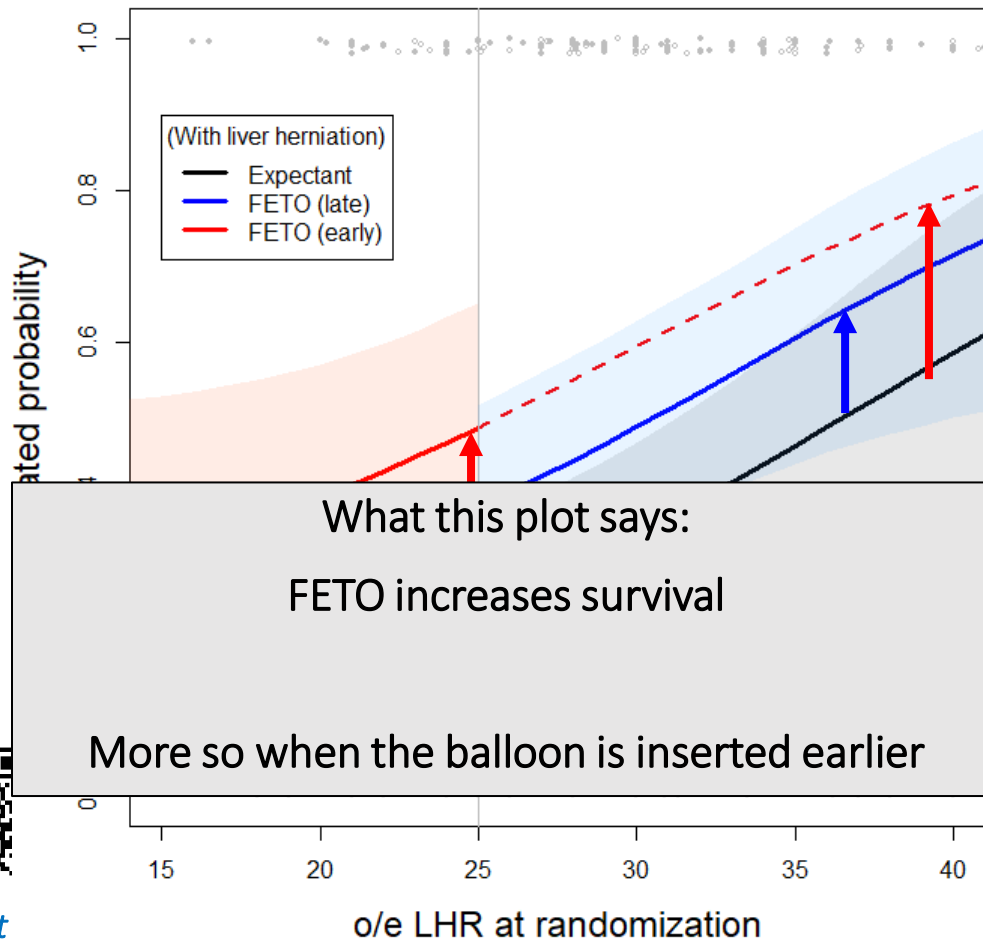
Deprest et al,
NEJM 2021a, 2021b

- Significant increase survival ($p < .005$)
- Increase risk (P) PROM & prematurity
- No obvious other differences

- Non-significant increase survival ($p = 0.059$)
- Increase risk (P) PROM & prematurity
- No obvious other differences



Analysis **pooled** data: survival

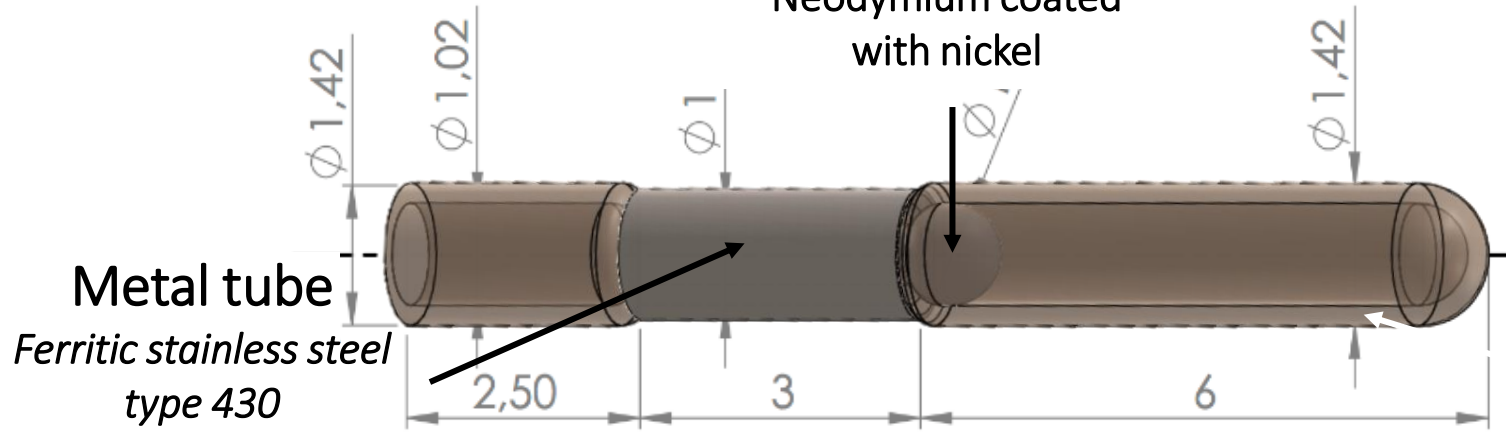


- To study heterogeneity of treatment effect by
 - severity (O/E LHR)**
 - gestational age at FETO**
- Penalized regression with covariates FETO (or not), early occlusion, o/e LHR, liver herniation, trial (n=291, ITT analysis)
- Displayed:
 - Full lines: observations
 - Dotted lines: modeled
- Prematurity will increase as well

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

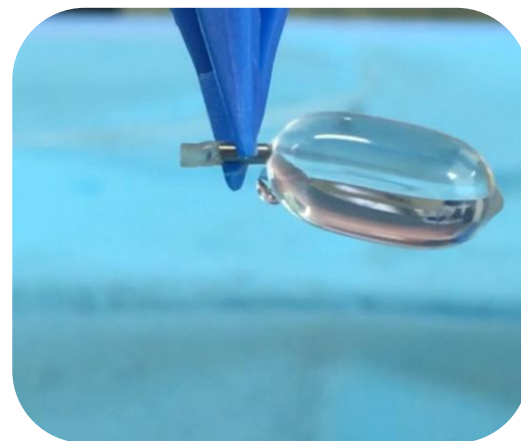
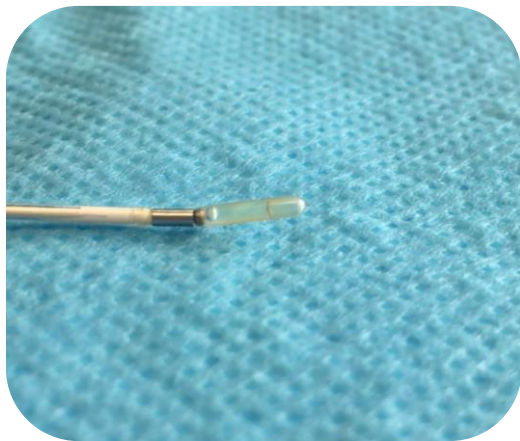
“Smart” TO balloon

Magnetic ball
Neodymium coated
with nickel



Metal tube

Ferritic stainless steel
type 430

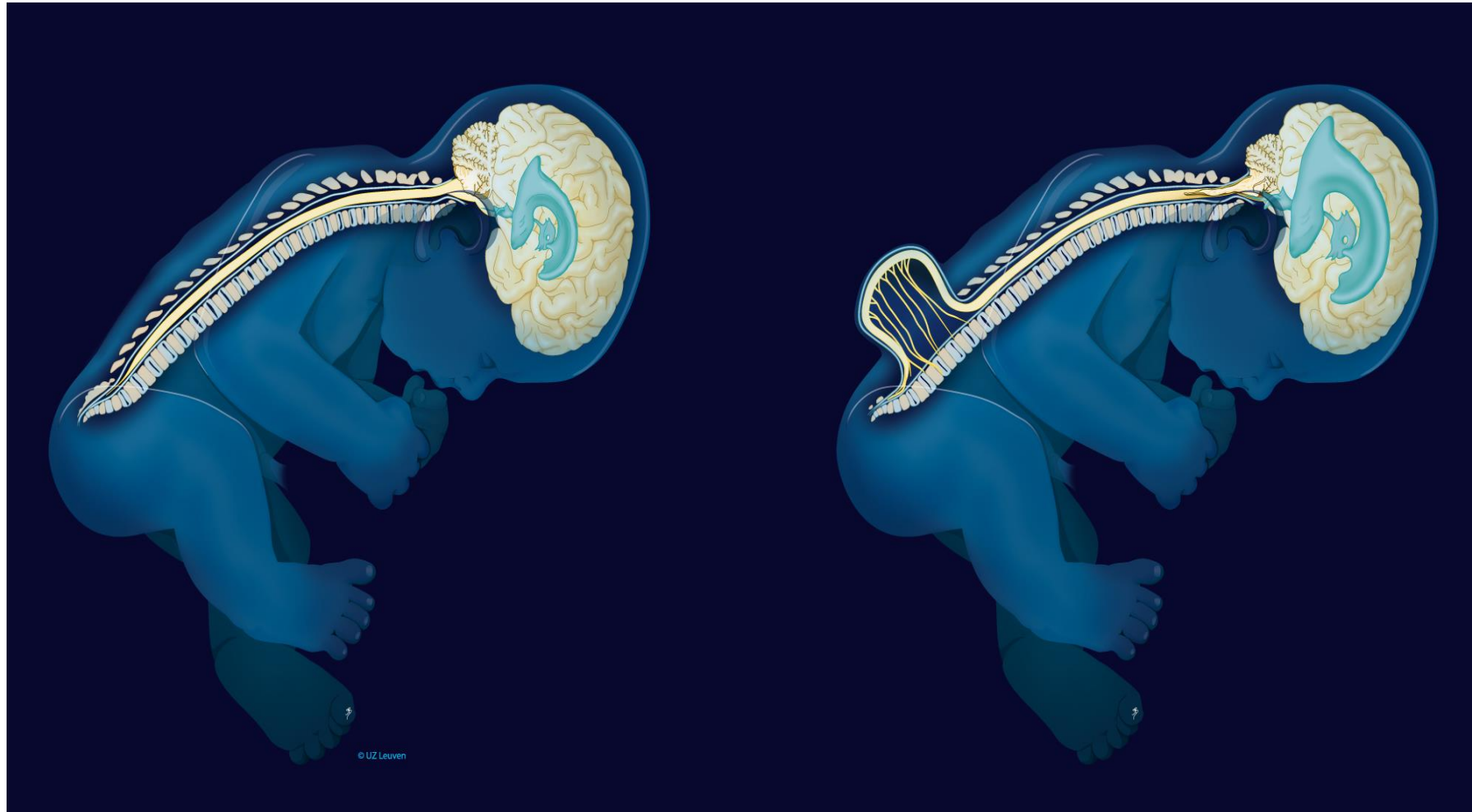


Phase I – trial half way
23/46 patients



Basurto, Sananes & Deprest, UOG 2020
Basurto, Sananes & Deprest, UOG 2021
Sananes, Benachi, Deprest, Sc Rep 2023

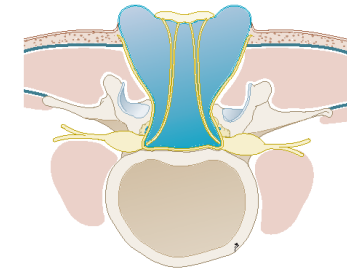
Spina bifida surgery



Prenatal Phenotype Spina Bifida

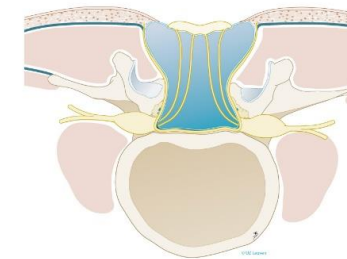
Brain changes: "lemon & banana"

Spinal lesion



Cystic lesion:
myelomeningocele

Nicolaidis, Lancet 1986 : midgestation
Lemon sign = scalloping frontal bones
Banana sign = curved cerebellum, no fluid
BPD < 5th centile in 61%
Ventriculomegaly in 86%



Flat lesion
myeloschisis

4.9/10,000 in Europe
 3,17/10,000 in USA
 30% reduction by folic acid



“Natural” history



1. “Local effects”

- Pelvic floor dysfunction
- sensorimotor function loss

2. “Brain effects”:

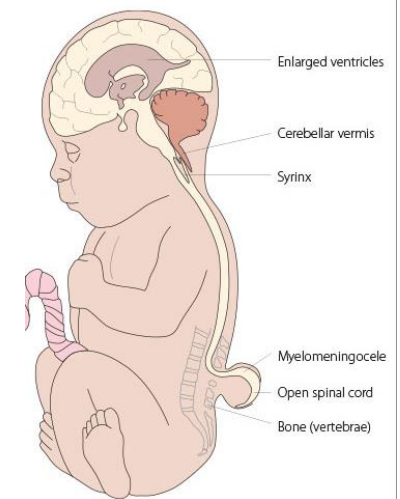
- Chiari type II: >75%
- ventriculo-peritoneal shunt in 50¹ to 80%²

3. Social & emotional impact

- Patient
- family

4. Long-term survival : 70% or more

- hydrocephaly and hindbrain herniation
- renal dysfunction



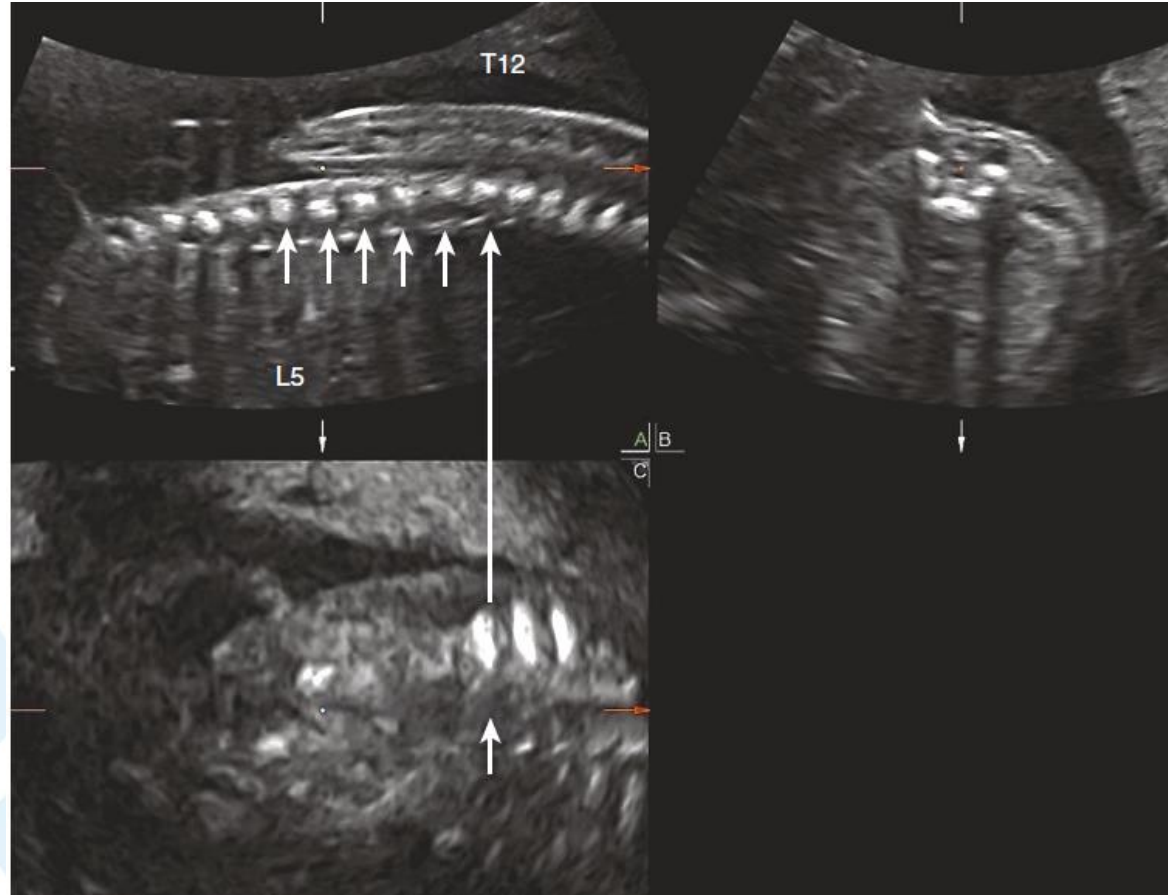
²Peranteau, *Curr Opin Obstet Gynecol* 2016
Tennant, *Lancet* 2010
Mitchell, *Lancet* 2004

¹Thompson, *Ped Child Res* 2014

¹Chakraborty et al, *J Neurosurg Ped* 2008



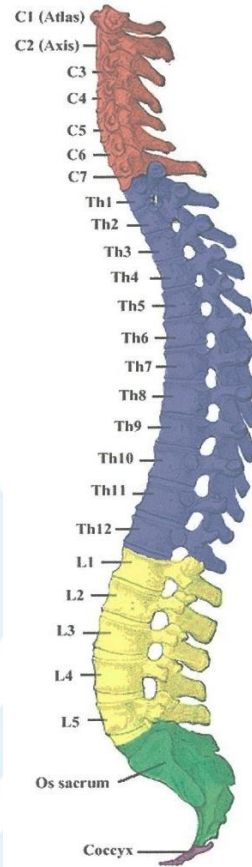
Spine severity: anatomical level



12th rib is reference point

But: 6% have abnormal number of ribs

Images: *De Catte L et al, Chapter 28. Fetal Medicine (Pandaya Edr, 2019)*



Thoracic lesions

Kyphosis, spinal surgery: 62%
Sitting problems
~ 100% shunt rates

> L2: 80% sexual dysfunction
≥ L3: unlikely to walk
L4: 60% will walk
L5: 90% will walk

S2 – S4
Urinary and fecal incontinence:
ICS & enemas

Cochrane et al, FDT 1996

Bowman, Ped Neurosurg 2001

Bruner & Tulipan, UOG 2004

Cass, J Urol 1986

Thompson, Prenat Diagn 2009

Woodhouse, Pediatr Nephrol 2008

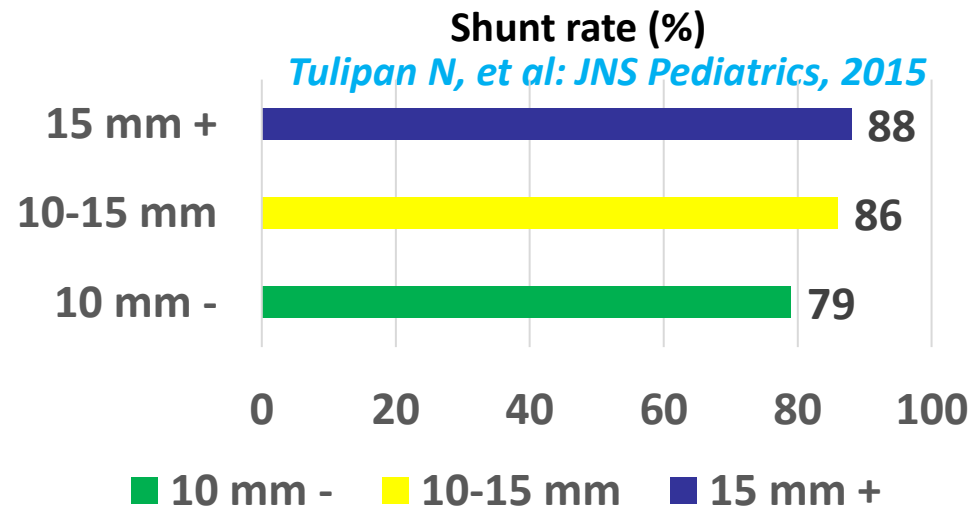
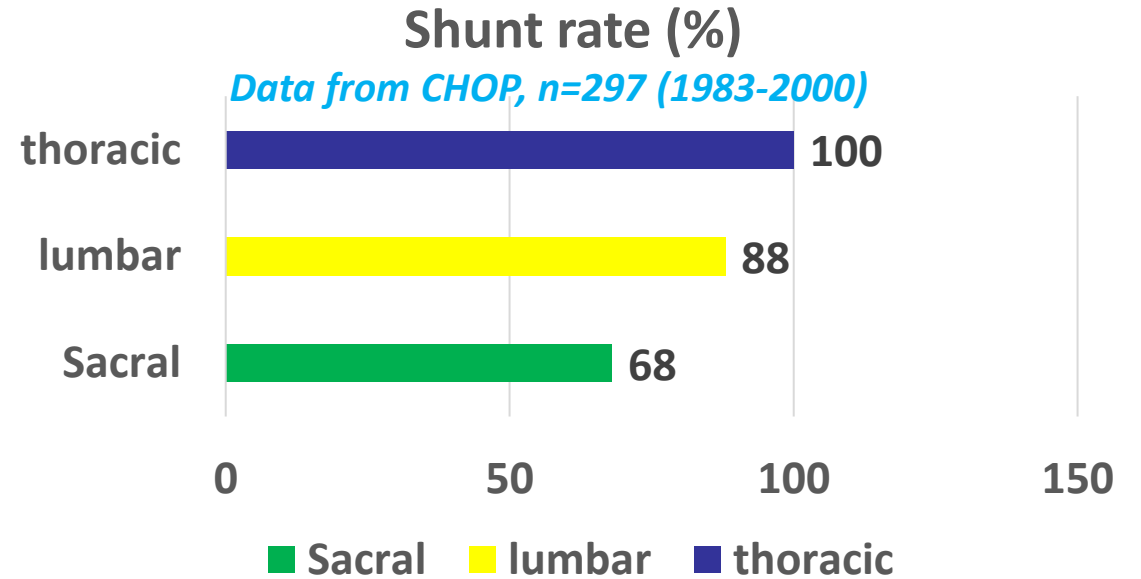


Personalized prediction

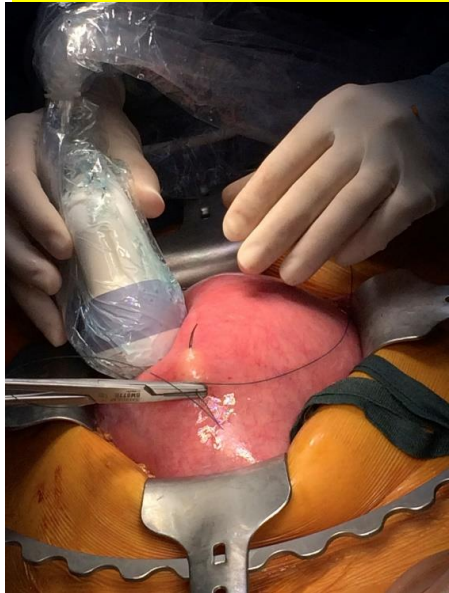


70% have *normal intellectual development (IQ>80)*
(Oakshot, BJ Gen Pract 2003)

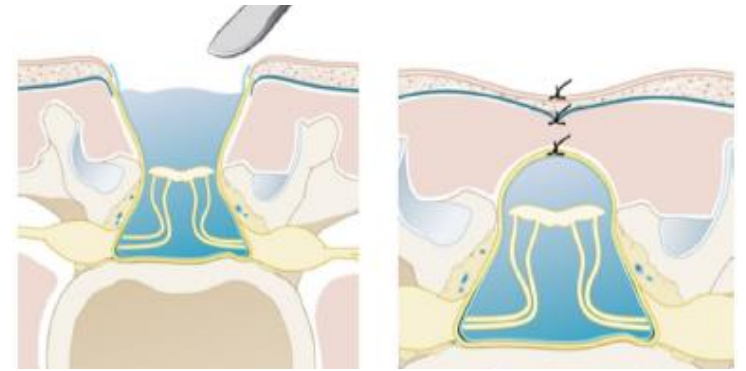
Hydrocephalus or problems with its management, is predictor: in its absence normal development *(Barf, Dev Med Child Neurol 2003)*

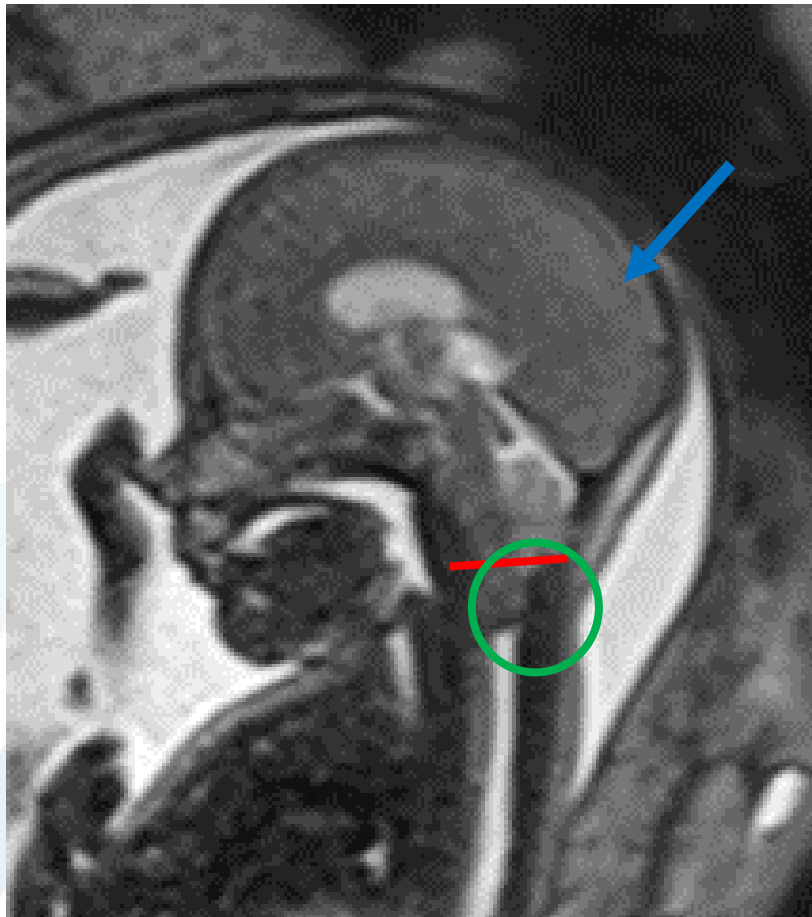


Standard technique: hysterotomy (2012)



Laparotomy
Uterine exposure
Stapled hysterotomy
Tacking of membranes





Reversal predicts later need for shunting (OR 0.19; 95 % CI 0.4-0.9) and motor function
Zarutskie, UOG 2019; Vonzun Ultras Med 2020, Correone, PND 2021



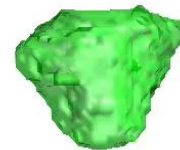
Aertsen M et al, AJNR 2019

Other signs: re-establishment
interpeduncular angle

Sepulveda, PND 2021

Cerebellar shape restored
Reversal of hindbrain herniation
Volume increase

Cerebral Shape Index (gyrification) also changes



“MOMS” Randomized Controlled Trial (2012)



12 months outcomes	Prenatal surgery	Postnatal surgery
Shunts	68%	98%

30 months outcomes	Prenatal surgery	Postnatal surgery
Walking independently	42%	21%

Management of Myelomeningocele Study (MOMS) - [Adzick, NEJM 2021](#)

5-10 years outcomes	Prenatal surgery	Postnatal surgery
Shunt placement	49%	85%
Shunt revision	23%	60%

Walking independently	45%	11%
Unable to walk	7%	20%

CIC @ 5-10 years	62%	60%
Voiding volitionally	24%	4%

Learning curve

CUSUM analysis
on raw data **expert** centers
(Philadelphia, Sao Paulo, Houston, Poland, UC Davis)

Learning curve open repair : **35**
Minimally invasive: **≥56-57**

Several teams have been able to reproduce this
Including Leuven (2012) and London (2016) teams



News

Spinal surgery for babies in the womb on the NHS

22 December 2018

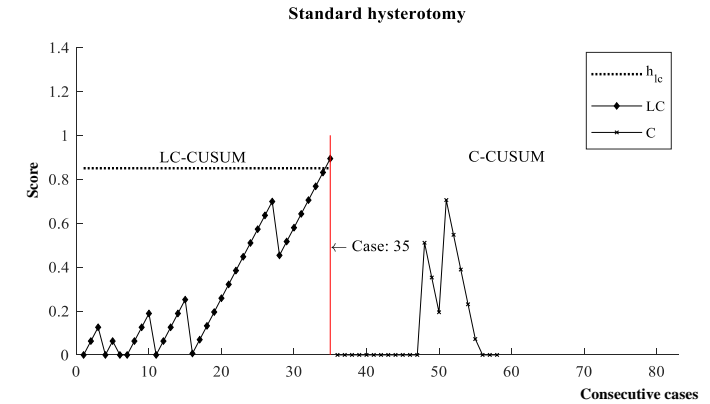
Innovation Long term conditions Maternity

Spinal surgery for spina bifida for babies in the womb is among new, innovative treatments that will be routinely available on the NHS for the first time, NHS England announced today.

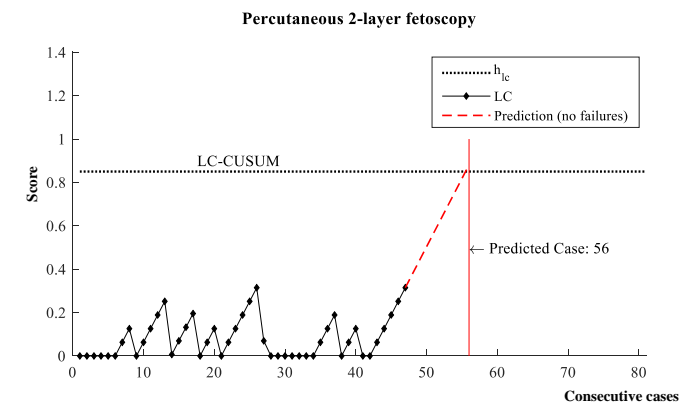
The cutting edge procedure for unborn children with spina bifida, whose spine and spinal cord do not develop properly, allows pregnant women to be treated closer to home and their families.

The surgery involves repairing the spinal tissue while the baby is still in the womb, which can reduce illnesses including bladder, bowel and kidney conditions later in life, and improve walking ability.

The life-changing procedure is among several new treatments that are being made routinely available on the NHS.



Joyeux et al, UOG, 2019



Maternal	MOMS trial ^{full cohort}	Leuven
GA at birth	34.0 ± 3.0	35.5 (34.0-36.6)
% delivering < 30 weeks	11%	6%
Uterine rupture	0%	0%
Uterine dehiscence	11.4 %	9%
Abruptio	6.6 %	1%
Pulmonary edema	5.5%	1%
Chorio-amnionitis	2.2%	1%
12 months outcomes	MOMS trial ^{full cohort}	Leuven (n=69)
Actual shunt rates	44%	46%
30 months outcomes	MOMS trial ^{full cohort}	Leuven (n=27)
Walking independently/aids	73%	96%
Wheelchair	28%	4%

Results MOMS trial can be reproduced – [Möhrlen, FDT 2020](#); [Vergote, UOG \(2023\)](#)

**The MOMS data are reference and used by NHS
to commission the service based on competitive proof of experience & outcomes**

Reducing incision



Hysterothoracotomy – 6-7 cm
Adzick, 2012

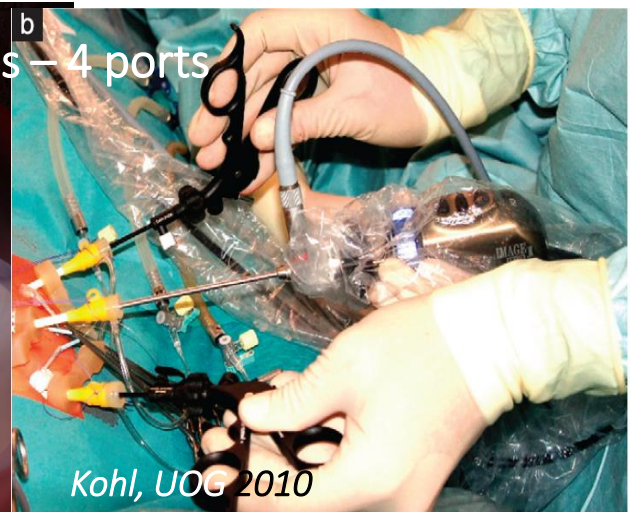


Mini-hysterothoracotomy – 3-4 cm
Botelho, 2017



Percutaneous – 4 ports

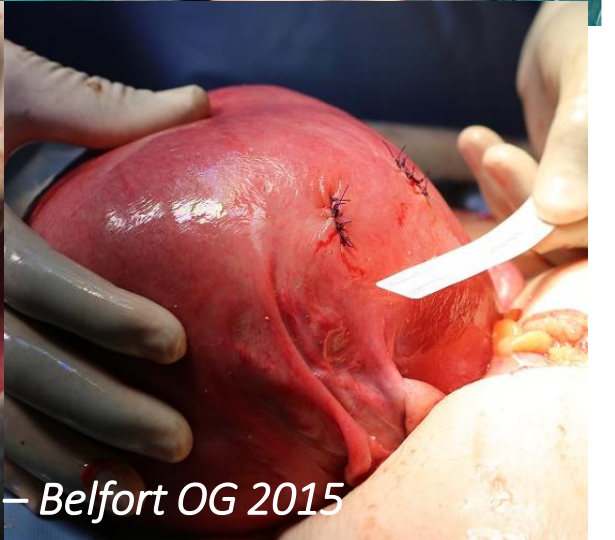
Pedreira & Quintero, 2010



Kohl, UOG 2010



Exposed uterus – *Belfort OG 2015*



Smaller incision: “mini”-hysterotomy



We moved to mini-hysterotomy in 2020

The surgical procedure is reproducible
Prematurity can be reduced
Vaginal delivery ?

Deprest & Peralta (AJOG 2023)
Matched (1:1) controlled study by:
lesion level, GA at operation, lesion type

Reduces membrane rupture Reduces prematurity		
GA at birth	34.1 ± 3.1	35.3 (23.7–39.9)
PPROM	46%	28.3%

At least same neuroprotective effect		
CSF leakage	13%	3.4%
Shunts placed	44%	14%
Walking	45%	36%

Avoids increased uterine rupture risk		
Intact	51%	95%
Thinning	41%	0%
Dehiscent	8%	5%

Significant later (p=0.014) delivery		
GA at birth	34.9 (33.5-36.5)	36.2 (34.2–37.5)

Reducing incision



Hysterotomy – 6-7 cm
Adzick, 2012

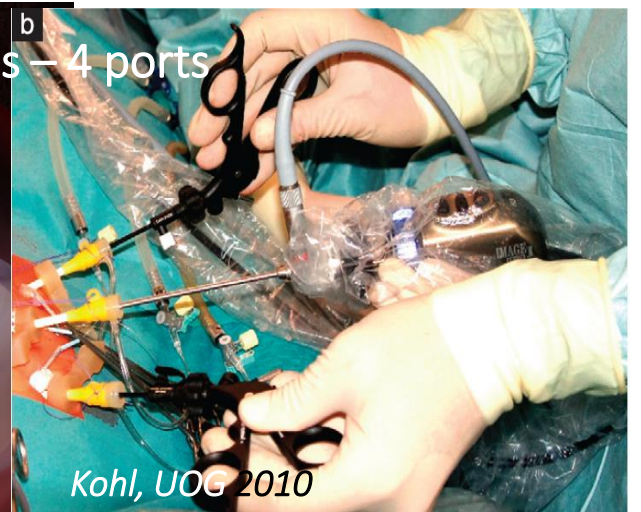


Mini-hysterotomy – 3-4 cm
Botelho, 2017



Percutaneous – 4 ports

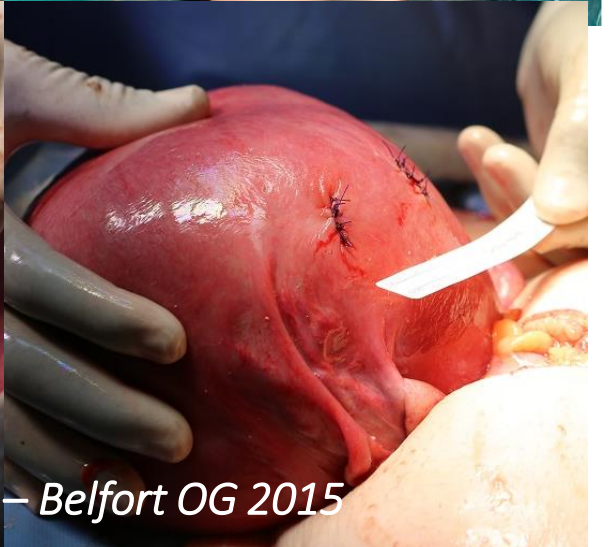
Pedreira & Quintero, 2010



Kohl, UOG 2010



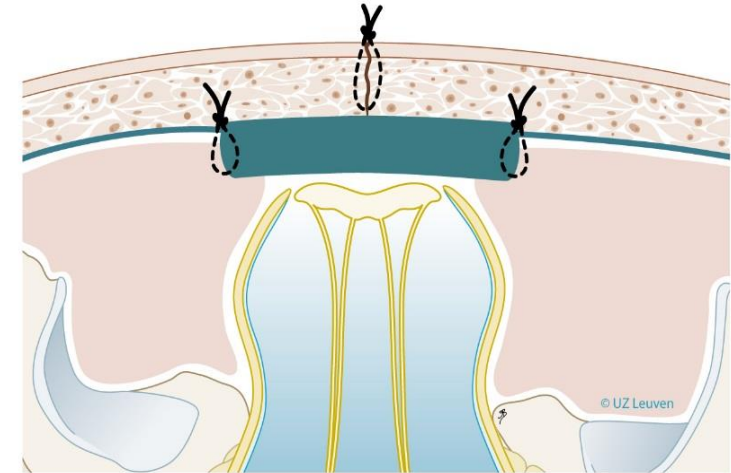
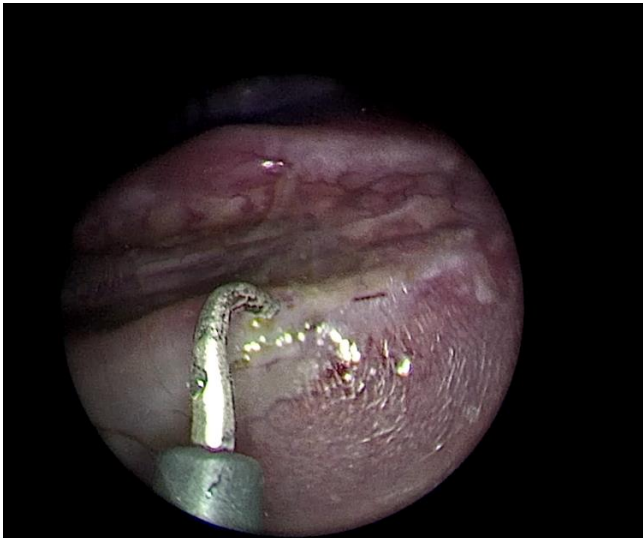
Exposed uterus – *Belfort OG 2015*



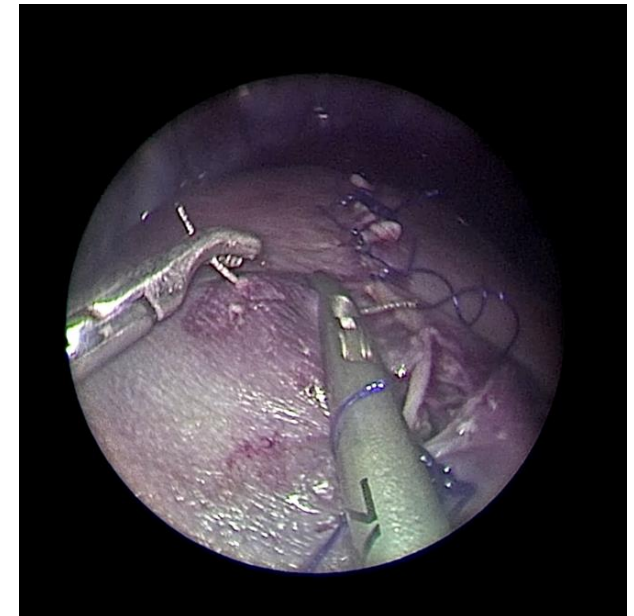
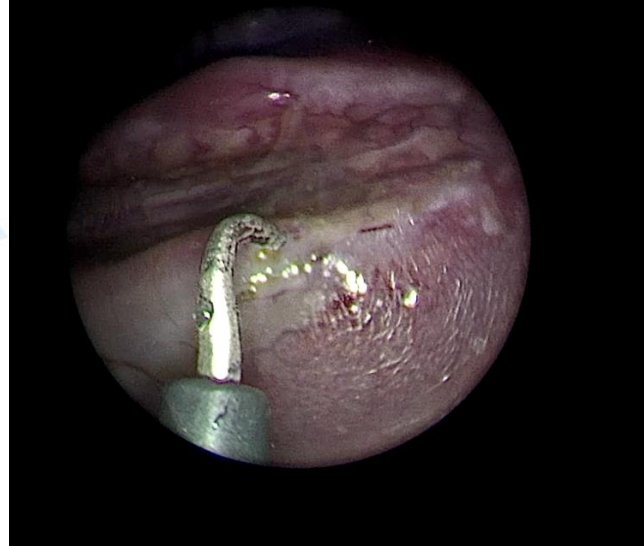
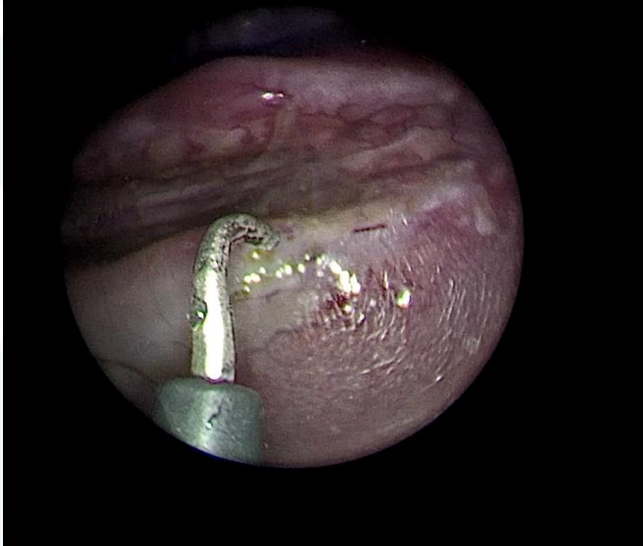


UZ
LEUVEN

Fetoscopic repair: your patient is offered this option

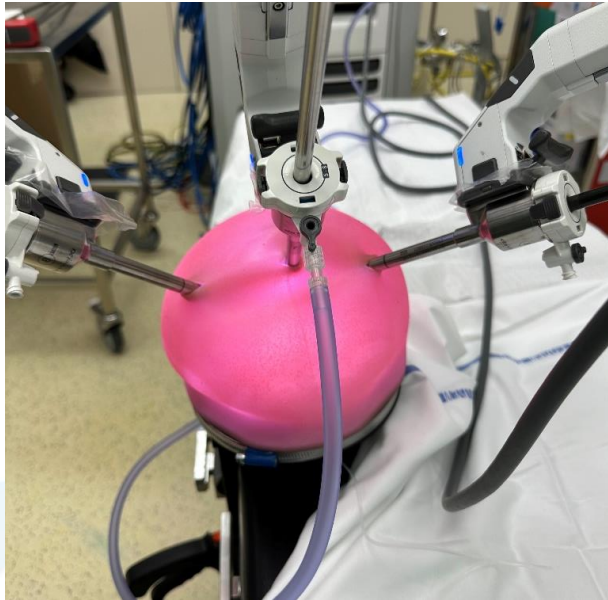


Pedreira (Lapa), AJOG 2016





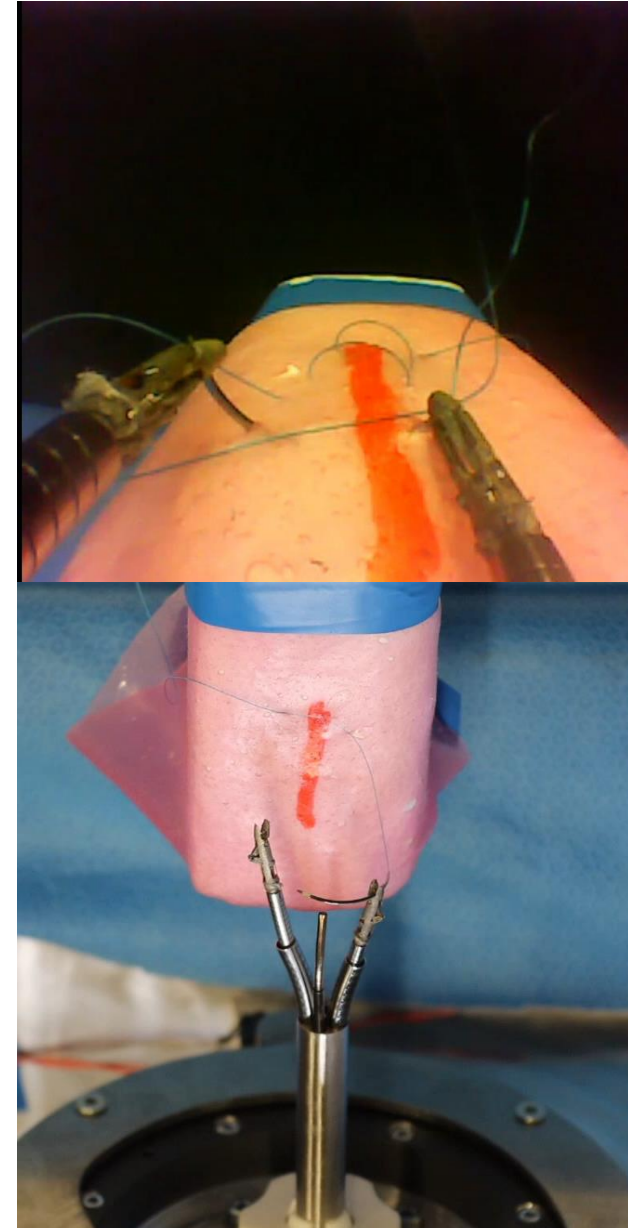
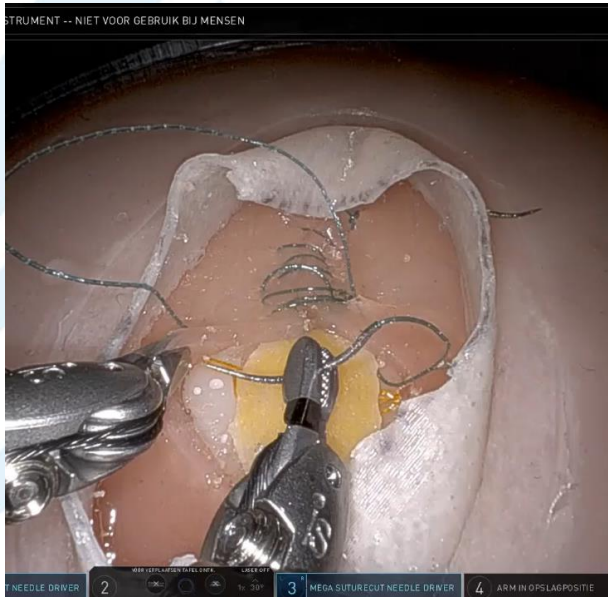
Development towards robotic surgery ?



3D vision
More degrees of freedom
Reduces tremor

Instruments still
too large

Towards a
single orifice,
small diameter
robot

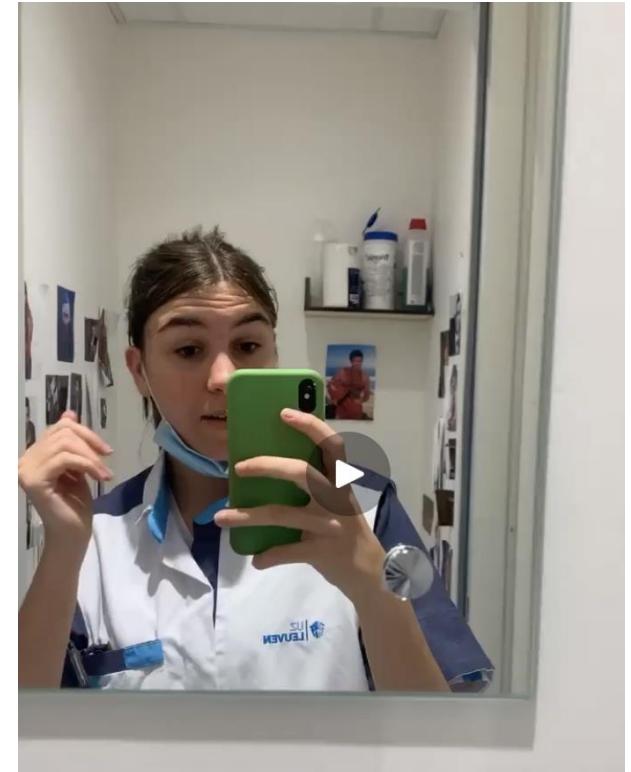




Thank you!



The Fetal Medicine Team Leuven



First Belgian FETO patient, born prematurely,
now doing internship in our hospital