Session 3: The Fetus with CDH
Chairs: Alexandra Benachi and Anthony Johnson

27th April 15.30 – 17.30

8 A core outcome set for perinatal interventions for congenital diaphragmatic hernia

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75 Fetal Brain Development in Congenital Diaphragmatic Hernia (CDH)

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84 Ultrasound prediction of survival in CDH: validation of the current algorithm in the TOTAL trial population

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115 Fetoscopic Endoluminal Tracheal Occlusion Balloon Related Complications

David Basurto[1], Kanokwaroon Watananirun[1], Francesca Maria RUSSO[1], Anne DEBEER[2], Luc DE CATTE[1], Liesbeth LEWI[1], Roland DEVLIEGER[1], Jan DEPREST[1,3]
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127 Prenatal Brain Maturation in Neonates with Congenital Diaphragmatic Hernia (CDH)

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A core outcome set for perinatal interventions for congenital diaphragmatic hernia

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Background

Core outcome sets (COS) enable future trials to measure identical outcomes, leading to higher-quality trials and facilitating comparison, contrasting and combination of trial results, hence reducing waste of time and resources in research. Such a set is currently not available for congenital diaphragmatic hernia (CDH), yet urgently needed as an increasing number of (perinatal) interventions are being evaluated. We aimed to develop a COS for clinical studies reporting pre- and neonatal outcomes for perinatal interventions for CDH using a validated consensus-building method.

Methods

An international steering group comprising leading maternal-fetal medicine specialists, neonatologists, pediatric surgeons, patient representatives, researchers and methodologists, guided the development of this COS. Potential outcomes were collected through a systematic review and entered into a two-round online Delphi survey. Stakeholders with experience with the condition, scored outcomes based on their relevance. Outcomes that fulfilled the a priori defined consensus criteria, were subsequently discussed in online breakout meetings. In a consensus meeting, the results were reviewed and the final COS was defined.

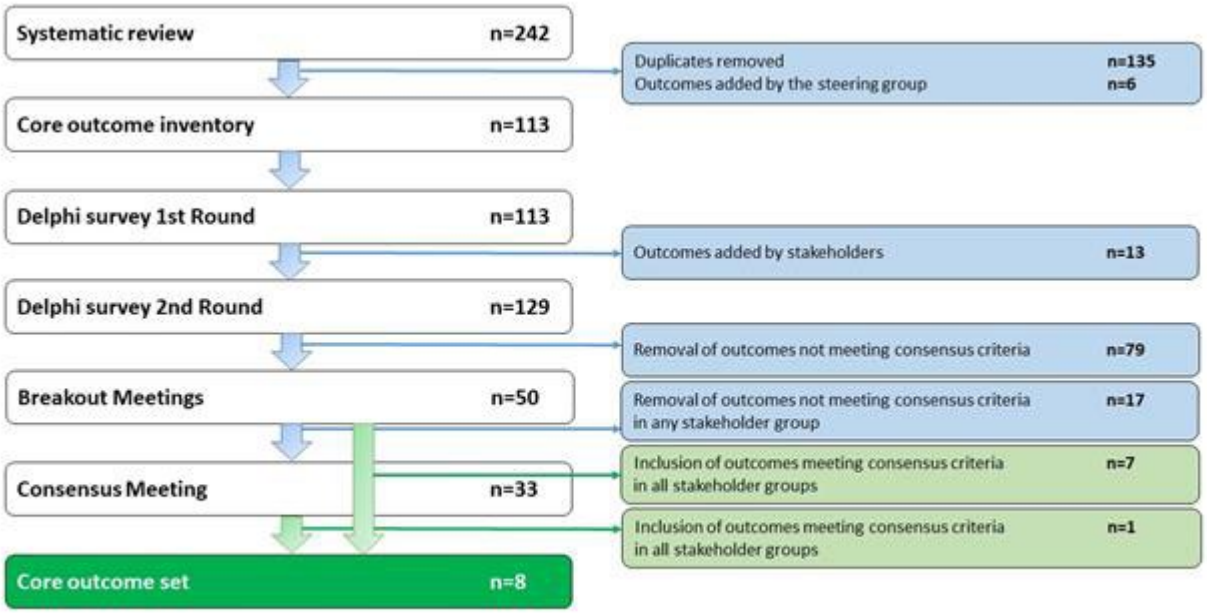
Results

Two hundred and twenty one stakeholders participated in the Delphi-survey and 198 completed both rounds (90%). Fifty outcomes meeting the consensus criteria were discussed and rescored by 78 stakeholders in the breakout meetings. During the consensus meeting, 93 stakeholders eventually agreed on eight outcomes constituting the final COS. Included maternal and obstetric outcomes were maternal morbidity related to the intervention and gestational age at delivery. Fetal outcomes were intra-uterine death, interval between intervention and delivery and lung development in utero. Finally, neonatal outcomes included neonatal mortality, pulmonary hypertension and the use of extracorporeal membrane oxygenation.

Conclusion

We developed a COS for studies on perinatal interventions in CDH with relevant stakeholders. Its implementation will facilitate comparison, contrasting and combination of trial results, enabling research to guide clinical practice.

Images


Systematic review n=242
Duplicates removed n=135
Outcomes added by the steering group n=6
Core outcome inventory n=113
Delphi survey 1st Round n=113
Outcomes added by stakeholders n=13
Delphi survey 2nd Round n=129
Removal of outcomes not meeting consensus criteria n=79
Breakout Meetings n=50
Removal of outcomes not meeting consensus criteria in any stakeholder group n=17
Consensus Meeting n=33
Inclusion of outcomes meeting consensus criteria in all stakeholder groups n=7
Inclusion of outcomes meeting consensus criteria in all stakeholder groups n=1
Core outcome set n=8

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Fetal Brain Development in Congenital Diaphragmatic Hernia (CDH)

Dr Isabella Fabietti[1], Dr Sara Savelli[2], Dr Anita Romiti[1], Dr Roberta Vicario[1], Dr Giulia Grassini[1], Dr Laura Valfrè[1], Dr Paola Giliberti[1], Dr Irma Capolupo[1], Prof Francesco Morini[3], Prof Pietro Bagolan[1], Dr Leonardo Caforio[1]

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Background: It is reported that many infants with CDH have evidence of brain injury on postnatal brain magnetic resonance imaging (MRI). It is not known whether this injury already occurs in utero. The objective of this study is to assess prenatal brain morphometry and cortical development in CDH using fetal MRI.

Methods: We retrospectively reviewed all fetuses with CDH followed between 2014 and 2021. Those who had brain MRI were included in the study. Foetuses who underwent prenatal MRI for disorders other than CDH, and had the brain included, served as controls. All fetuses were imaged using a 1.5T MRI scanner. The two groups were compared for the following variables: brain morphometry (fronto-occipital diameter, cerebral biparietal diameter, bone biparietal diameter, transverse cerebellar diameter, and anteroposterior and craniocaudal cerebellar vermis dimensions) and cortical fissure (CF) depths (parietooccipital, lateral and cingulate fissures) and insular depth. CF were measured and corrected by biparietal diameter (BPD), obtaining a ratio (CF/BPD) for each fissure measurement to perform the statistical analysis. Fetuses with known syndromes were excluded from the study.

Results: A total of 53 fetuses with isolated CDH and 49 controls were included in the study. Table shows main findings.

Conclusions: Fetuses with CDH present significant cortical sulcation differences as compared to controls, with deeper cingular fissure and reduced insular depth. Further studies are needed to define the congenital or secondary nature of these findings.

Images

	CDH	Controls	p
Transverse cerebellar diameter (mm)	39 (24-51)	41 (30-49)	0.1533
Anteroposterior vermis length (mm)	13 (9-17)	13 (9-16)	0.3214
Craniocaudal vermis length (mm)	18 (13-25)	19 (13-23)	0.7155
Parietoccipital fissure depth/BPD	0.09 (0.07-0.13)	0.09 (0.05-0.15)	0.6492
Lateral fissure depth/BPD	0.16 (0.13-0.21)	0.16 (0.12-0.19)	0.5901
Cingular fissure depth/BPD	0.06 (0.03-0.10)	0.04 (0.03-0.09)	**<0.0001**
Insular depth/BPD	0.27 (0.24-0.33)	0.28 (0.23-0.33)	**0.0149**

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Ultrasound prediction of survival in CDH: validation of the current algorithm in the TOTAL trial population

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Background
One potential criticism on the antenatal ultrasound prediction model is that it is based on historical data and an unstandardized postnatal management model. We evaluated the performance of the proposed model among the TOTAL trial population.

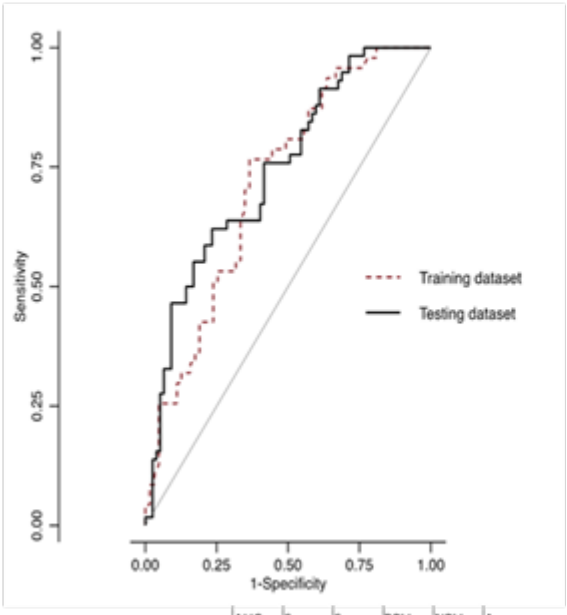
Methods
From both the cohort used to develop the algorithm (training dataset) and the TOTAL trial cohort (testing dataset), we selected cases with isolated, left-sided diaphragmatic hernia with severe or moderate lung hypoplasia born in European centers (N=110 and 135, respectively). External validation of the model was done by using a ROC curve analysis, sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy as discrimination methods. Calibration was performed by plotting the observed vs predicted survival in the testing dataset and compared using the Hosmer-Lomeshow test for goodness-of-fit.

Results
Gestational age at delivery (38.1±1.9 vs 37.6±2.2weeks, p=0.1) and o/eLHR (29.0±7.3% vs 28.4±6.8%, p=0.5) were comparable in the two cohorts. Liver herniation was more frequent in the testing population (81% vs 57%, p<0.001).
In the testing dataset, a higher o/eLHR (OR 1.13, 95%CI 1.07-1.21) and the absence of liver herniation (OR 3.18, 95%CI 1.23-8.26) remained independent predictors of survival.
The discrimination of the original model was similar for both datasets (AUC 72% vs 75%; p=0.620, Figure1A). Calibration analysis showed that the model significantly underestimates survival (p=0.035). More specifically, survival was overestimated in the most severe cases and underestimated in the rest of the population (Figure1B).

Conclusions
In the unbiased TOTAL trial European cohort, o/eLHR and liver herniation remain independent predictors of survival. The prediction model so far slightly overestimates survival in the most severe cases and underestimates it in the other cases.

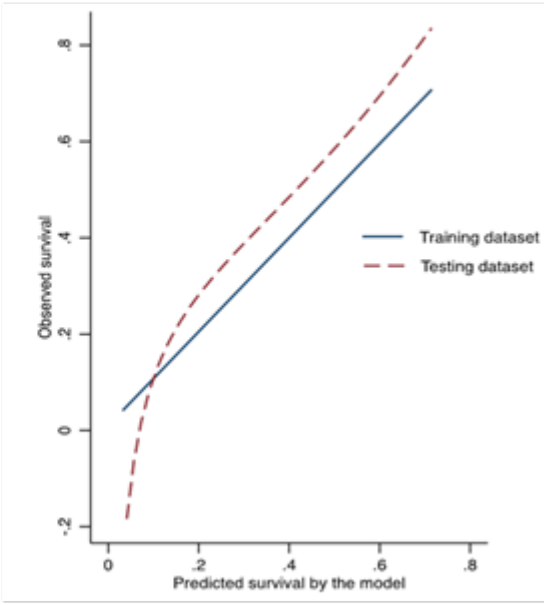
Graph

1A



	AUC	Se	Sp	PPV	NPV	Accuracy
Training dataset	72%	55%	67%	55%	67%	62%
Testing dataset	74%	59%	78%	67%	71%	70%

1B



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Fetoscopic Endoluminal Tracheal Occlusion Balloon Related Complications

David Basurto[1], Kanokwaroon Watananirun[1], Francesca Maria RUSSO[1], Anne DEBEER[2], Luc DE CATTE[1], Liesbeth LEWI[1], Roland DEVLIEGER[1], Jan DEPREST[1,3]

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Abstract

In a cohort of congenital diaphragmatic hernia (CDH) fetuses that underwent Fetoscopic Endoluminal Tracheal Occlusion (FETO), we want to investigate (1)the incidence of balloon-related complications (BRC), and (2)to identify potential predictors for BRC.

Study Design:

Retrospective study in left and right CDH fetuses that underwent FETO at UZ Leuven between 2002 and 2021. Investigated BRC were the presence of spontaneous balloon deflation, presence and location of balloon remnants at postnatal X-ray. The incidence of tracheomalacia and its resolution was investigated among survivors. Finally, we investigated correlations between BRC and potential predictors. Recorded variables were: gestational age(GA) at FETO, FETO procedure length, balloon type, occlusion days, unplugging-birth interval, GA at delivery, and ventilation days.

Results:

A total of 209 FETO procedures were included. Spontaneous balloon deflation occurred in 5% of the cases. There was no correlation with the type of balloon. At d1 postnatal x-ray, the metallic remnant of the balloon was present within the body in 31% of the neonates (37% airways, and 63% gastrointestinal(GI) tract). In all survivors, the balloon remnants within the airways remained in place, however, without reported consequences. On the contrary, all survivors evacuated the balloon remnants from the GI at a median of 6.5 (IQR 4 – 8.5) days. There were no correlations with those findings.

97 infants survived and were followed until 7.9 (IQR 2.8-49.6) months. 18% were diagnosed with tracheomalacia at 211 (IQR 29-456) days after birth (bronchoscopy 71% or clinically 29%). At the last follow-up, 82% were asymptomatic. There was no correlation between the investigated variables and the occurrence of tracheomalacia.

Conclusions:

FETO balloon-related complications are not uncommon. Spontaneous balloon deflation occurs in 5%. 1 out of 3 infants will have balloon remnants at the GI or airways, however without apparent consequences. Tracheomalacia is common but resolves in most cases.

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Prenatal Brain Maturation in Neonates with Congenital Diaphragmatic Hernia (CDH)

Dr. Sandy Johng[1], Daniel Licht[1], Holly Hedrick[1], Natalie Rintoul[1], Rebecca Linn[1], Rui Xiao[2], Shavonne Massey[1]
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Background: CDH infants are at increased risk of neurodevelopmental impairment (NDI). It is unknown whether NDI is due to congenital differences in neurodevelopment, or sequelae of critical illness. We assessed prenatal brain maturation according to a fetal Total Maturation Score (fTMS), to investigate neurodevelopment prior to critical illness. This study is the first to examine fTMS in CDH.

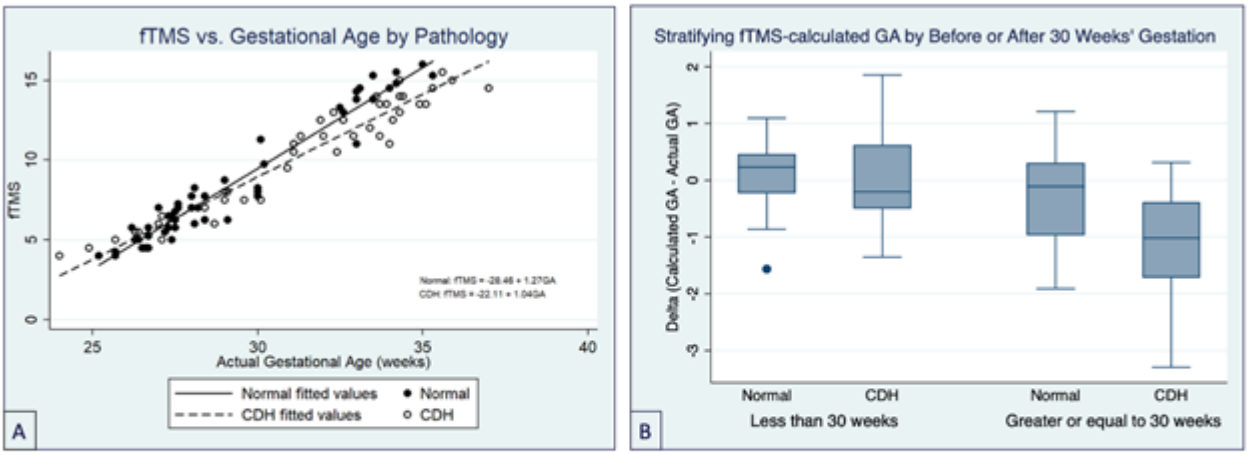
Methods: We conducted a retrospective cohort study using data from a quaternary single-center registry. Our study cohort consisted of neonates with CDH between 2014 and 2020 who had a prenatal neurologic MRI between 25 and 35 weeks gestational age (GA). CDH fTMS were compared to historical controls. The relationship between fTMS and actual GA was assessed with linear regression models. Key CDH variables were tested as potential modifiers of fTMS using linear regression models. Early (<30 weeks) versus late (≥30 weeks) fTMS were compared with a t-test.

Results: 48 infants met inclusion criteria for the prenatal study population, 41 of whom were inborn and in the postnatal study population. Compared with controls (N = 48), CDH fTMS were significantly delayed (p-value <0.001), and this delay emerged after 30 weeks' gestation (p-value = 0.001) (Figure 1). There was no significant difference in fTMS based on CDH severity, intrathoracic liver position, right versus left CDH, gender, ECMO therapy, or in-hospital mortality. CDH placentas had a higher proportion of fetal vascular malperfusion (56%) compared with historical controls (7-20%).

Conclusions: Prenatal brain maturation in CDH infants is delayed after 30 weeks' gestation, potentially due to placental pathology given a high proportion of fetal vascular malperfusion. The impact of prenatal brain immaturity needs further investigation, starting with reporting neurodevelopmental outcomes in our cohort. It is crucial to understand how placental pathology influences neurodevelopment, and investigate potential modifiable factors that could improve prenatal health in the CDH population.

Images

FIGURE 1:



(A) The relationship between fTMS and actual gestational age in CDH infants versus normal controls was assessed using linear regression models, and the slopes of the cohorts' correlations were found to be significantly different (CDH 1.04, Control 1.27, p <0.001). On visual inspection of the correlations, the divergence in fTMS between CDH infants and normal controls appeared to occur after 30 weeks' gestation.

(B) A comparison of delta values (Calculated Gestational Age minus Actual Gestational Age) demonstrates that, when stratified by gestational age less than or greater or equal to 30 weeks' gestation, the delay of fTMS in CDH infants was only significant at greater or equal to 30 weeks' gestation. An unpaired t-test comparing delta values between CDH and control infants was only significantly different at greater or equal to 30 weeks' gestation (Less than 30 weeks: Control delta mean 0.11 versus CDH delta mean 0.02, p-value = 0.65; Greater or equal to 30 weeks: Control delta mean -0.20 versus CDH delta mean -1.11, p-value = 0.001).