Thursday 28th April – Afternoon
Poster Screen 1:

14 Association between prenatal ultrasound parameters and survival in very preterm infants with congenital diaphragmatic hernia

Denise Oudshoorn[1], Francesca Russo[2], Jan Deprest[2], Florian Kipfmueller[3], Annegret Geipel[3], Thomas Schaible[4], Neysan Rafat[4], Anne-Gael Cordier[5], Alexandra Benachi[5], Nimrah Abbasi[6], Priscilla Chiu[7], Willem de Boode[8], Esther Sikkel[8], Nina Peters[1], Irwin Reiss[1], Philip DeKoninck[1,9]
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Mrs Jasmin Heath[1]
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Dr Rebecca Pulvirenti[1,2], Dr Miriam Duci[1], Dr M Schnater[2], Dr Francesco Fascetti Leon[1], Dr Paola Veronese[3], Dr Johannes J Duvekot[4], Prof RMH Wijnen[2], Dr Hanneke IJsselstijn[2], on behalf of the European Reference Network for rare Inherited and Congenital Anomalies (ERNICA)
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129 Prenatal brain development is altered in Right Congenital Diaphragmatic Hernia on ultrasound

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Association between prenatal ultrasound parameters and survival in very preterm infants with congenital diaphragmatic hernia

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Background: To assess the association between currently used ultrasound predictors and survival in very preterm born CDH infants. The primary aim was to improve evidence-based counselling for parents that are confronted with threatened preterm birth.

Methods: A retrospective cohort study including all infants with an isolated CDH that were live born ≤32.0 weeks of gestational age in seven high volume CDH centres between January 2009 and January 2020. The main outcome was survival to discharge and the survival rates were compared with the current prediction algorithm. Logistic regression analysis evaluated the association of observed to expected lung-to-head ratio (o/e LHR), side of the defect, and fetoscopic endoluminal tracheal occlusion (FETO) therapy with survival. The association of liver position and stomach position with survival was assessed for infants with left-sided CDH (LCDH).

Results: There were 50 CDH infants with a median gestational age at birth of 30+4 [IQR 29+1-31+2] weeks+days. In the total group, o/e LHR was associated with survival (OR 1.11, 95% CI 1.03-1.22; p=0.01), but FETO was not (OR 5.05, 95% CI 1.04-31.08; p=0.06); also, right-sided CDH (RCDH) had a lower survival (OR 0.12, 95% CI 0.02-0.65; p=0.03). Figure 1 depicts the survival rates per subgroup. For LCDH with expectant intra-uterine management, o/e LHR was associated with survival (OR 1.28, 95% CI 1.10-1.60; p=0.007). We observed a difference in survival based on stomach grades (p=0.03), but not based on liver position (p=0.13). All infants with RCDH had intrathoracic liver position and abdominal stomach position. FETO appeared to have a positive effect on survival in severe LCDH; this was less evident in RCDH.

Conclusions: Counselling of parents in case of imminent preterm delivery of an infant with CDH should be primarily based on the expected severity of pulmonary hypoplasia and side of the defect.

Graph

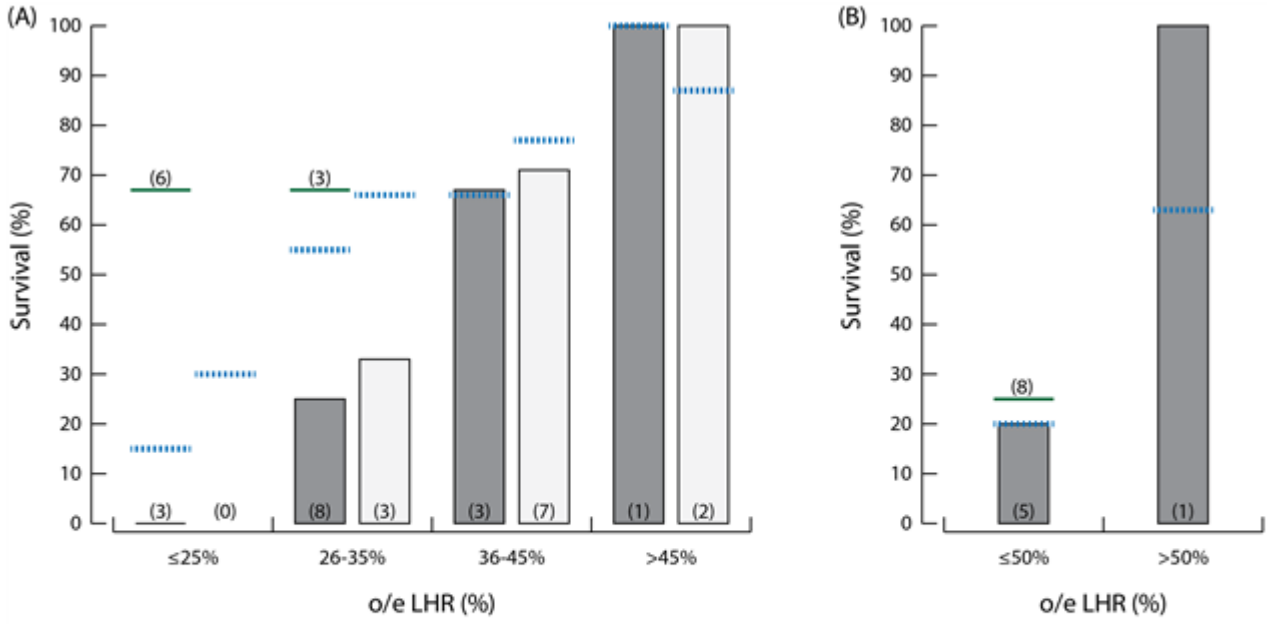

Figure 1 Survival rates in infants with isolated left-sided (A) and right-sided (B) congenital diaphragmatic hernia that did not receive fetoscopic endoluminal tracheal occlusion (FETO) therapy. The filled bars represent fetuses with intrathoracic liver position and the open bars represent fetuses with intra-abdominal liver position. Numbers per group are depicted between brackets. The blue lines represent historical data from Jani *et al* (2007) (A) and from Russo *et al* (2020) (B); the green lines represent the survival rates of infants that received FETO therapy. o/e LHR = observed to expected lung-to-head ratio.

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Postnatal Prediction Models in Newborns with Congenital Diaphragmatic Hernia: A Literature Review

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Background:

The predicted severity of CDH is often based on antenatal characteristics, however after birth newborns with CDH can have a discrepant clinical course and the degree of pulmonary hypertension, a major determinant of mortality in this population, can be poorly correlated with antenatal assessment. Consequently, the ability to generalise findings postnatally is limited, which is likely to become more relevant in the era of fetal interventions. Accurately predicting the risk of mortality postnatally may help to target therapies and counsel families. This review aimed to evaluate the reliability of postnatal prediction models, used in the first 24 hours of life, to predict risk of mortality.

Methods:

CINAHL, MEDLINE, EMBASE and Web of Science were searched between April 2020 and November 2021. The Cochrane Library, Ethos and PROSPERO were also searched. Studies were eligible if a prediction model was applied in the first 24 hours of life in newborns with CDH, with a primary outcome of mortality. CHARMS and PROBAST were used for data extraction and risk of bias assessment. Factors that could affect the reliability of the model's predictive performance were identified and narratively summarised.

Results:

Eight papers were eligible for inclusion, investigating eight different prediction models. They all showed good discriminative performances (C-statistic 0.74-0.97), but calibration measures were poorly reported. The reliability of their predictive performances were affected by the heterogeneity in defining and assessing prediction variables. There was a high risk of bias due to insufficient sample sizes, and insufficient reporting of data collection.

Conclusion:

The eight postnatal prediction models all demonstrated good discriminative performance, however, due to insufficient reporting of calibration measures and heterogeneity of the prediction variables recommendations for their use in clinical practice cannot be made. A large, prospective, UK multicentre study is required to reliably determine their performance within the UK CDH population.

Images

Prediction Models and Identified Themes				
Prediction Model	**Prediction Variable**	**Heterogeneity in defining and assessing variable**	**Subjectivity of variable**	**Variable threshold not generalisable to CDH population.**
CDHSG Probability of Survival (CDHSG-PS)	Birthweight			
	APGAR Score		√	√
Brindle Tool	Birthweight			
	APGAR score		√	√
	Congenital heart defect	√		
	Chromosomal abnormality	√	√	
Updated Brindle Tool	Birthweight			
	APGAR score		√	√
	Congenital Heart Defect	√	√	
	Chromosomal Abnormality		√	
	Intrathoracic Liver Position	√	√	
Perinatal Prognostic Index	Gestational age at diagnosis			
	Polyhydramnios	√	√	
	Observed/Expected Lung-to-head ratio		√	
	Blood gas measurements	√		
	FiO2			
	Mean Airway Pressure			
	Tricuspid Regurgitation	√	√	√
Score for Neonatal Acute Physiology II (SNAP-II)	Blood gas measurements	√		
	FiO_2			
	Blood pressure			√
	Temperature			√
	Urine output			
	Seizures		√	√
Wilford Hall Santa Rosa Prediction Formula (WHSRpf)	Blood gas measurements	√		
PF-PCO2 Tool	Blood gas measurements	√		
	FiO_2			
Oxygenation Index (OI)	Blood gas measurements	√		
	FiO_2			
	Mean Airway Pressure			

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PREGNANCY IN CONGENITAL DIAPHRAGMATIC HERNIA (CDH) SURVIVORS: A PILOT STUDY

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Background: With the advancement of neonatal intensive care an ever-increasing group of CDH patients is reaching adulthood. Subsequently, new challenges arise, e.g. obstetric management in female CDH survivors. To our knowledge, information has been restricted to personal episodic communication. To establish optimal counseling for future lifelong care, we performed a first evaluation of a cohort of females who underwent CDH correction to assess the prevalence and course of pregnancies.
Methods:For the purpose of this pilot study we retrospectively retrieved the medical records of all females born with CDH between 1975 and 1997 at two tertiary referral centers (The Netherlands, Italy). In all patients with a known obstetric history, we recorded information on CDH correction, follow-up, pregnancy course and delivery. Descriptive statistical analysis was conducted.
Results:Obstetric history data were retrieved for 16 patients; neonatal data was found in eleven of them. All neonates underwent laparotomy for CDH correction. Six patients (54%) had known respiratory morbidities (symptoms or abnormal lung function). More information on background, pregnancies and offspring are depicted in the Table. In all sixteen women, 34 spontaneous and four artificially induced pregnancies were reported. Thirteen pregnancies (34%) ended in miscarriage, two are currently ongoing. Twenty-three pregnancies resulted in delivery of 22 neonates, with one delivery being induced pre-term due to the patient's lung function deterioration. Median gestational age at delivery was 39/2 weeks (32/4–41/5). CDH recurred in two patients; one of them presented a first recurrence preconceptionally, which needed patch repair. A second recurrence occurred immediately after delivery, requiring a posterior suture of the existing patch. The second patient was asymptomatic and was monitored during pregnancy.
Conclusions:These preliminary data suggest that preconceptional counseling and multidisciplinary team pregnancy monitoring are essential in female CDH survivors. Further multicenter studies are necessary to assess the CDH impact on fertility, pregnancy and newborns' outcomes.

Images

	Primary closure	Patch repair	Unknown
Side diaphragmatic defect	2 left, 4 right	3 left, 2 right	5
Pregnancies *	15	15	8
Symptoms during gestation	0	Decrease in lung function (1)	0
Miscarriages *	2	8	3
Method of delivery	6 vaginal, 2 c-section, 3 unknown†	2 vaginal, 3 c-section, 1 unknown	2 vaginal**, 1 c-section, 2 unknown
Live births *	11	6	5**
Neonatal anomalies	Left-sided CDH (1)	0	Hypospadias (1)
Symptoms after delivery	0	CDH recurrence (1)	0
Current age of CDH patients (years, median)	37.5 (32-44)	32 (29-42)	32 (25-38)

*Each patient may have had one or more events; **One twin pregnancy; † Two pregnancies excluded due to absence of delivery data

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Heritable disorders of fibrous connective tissues in patients with Diaphragmatic Herniae: The relevance of genetic evaluation.

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Background: Congenital Diaphragmatic Hernia (CDH) is a congenital abnormality affecting diaphragm and lung development. CDH may occur as an isolated defect, but 40% of CDHs are in the setting of a genetic syndromes or associations. Etiology of CDH is largely heterogeneous, since multiple monogenic and chromosomal disorders are diagnosed in patients with CDH. Purpuse: to evaluate the incidence of heritable disorders of fibrous connective tissues in CDH patients referring to Bambino Gesu' Children Hospital follow-up program in 48 months. Methods: All our CDH patients undergo to a scheduled follow up. In the last four years we planned a genetic evaluation in all CDH patients after birth while still in the hospital. After discharge the follow up includes clinical-phenotypical examination, 2-Dimensional color-Doppler echocardiography, renal ultrasound examination, ophthalmological and audiometric examination. Patients with clinical suspect of Marfan or Ehlers-Danlos syndrome underwent specific genetic testing (targeted Next Generation Sequencing).

Results: 80 CDH patients had a genetic counseling in follow up program. 6/80 (7%) had clinical features of Marfan-like Syndrome, 12/80 (15%) of Ehlers-Danlos. Mean age at clinical diagnosis was 5-6 ys for both groups. In one patient with Marfan-like syndrome a heterozigous c.976C>T variant (Pro326Ser) in FBN2 gene has been identified, genetic testing is ongoing in the additional patients.

Conclusion: These results are underlining the need of clinical and genetic screening for disorders of fibrous connective tissues in selected patients with CDH, in order to perform specific follow up and prevention.

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Single center genetic evaluation in Congenital Diaphragmatic Hernia patients

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Background: Congenital Diaphragmatic Hernia (CDH) is one of the most common and severe birth defect. The genetic contribution to CDH are highly heterogeneous and incompletely defined. Numerous studies have been discussing the role of copy number variants (CNVs) in the ethiology of CDH. Both inherited and de novo CNVs are described to have a causative role in CDH and at least 10% of CDH cases are estimated to be caused by genomic imbalance.
Purpuse: This study includes 356 childrens with CDH treated in Our Center, Bambino Gesu' Childrens Hospital (April 2000 -December 2020).
Method: 121 CDH patients were analyzed by array comparative genomic hybridization (array-CGH) and 43 patients by Next Generation sequencing analysis (NGS).

Results: A total of 14 (11.5%) Copy Number Variant (CNV) classificated as VUS have been identified in 13 cases. In one case it regards the 8p23.1 deletion, already associated to CDH, and one patient had Maternal uniparental disomy of chromosome 14.
The NGS analysis identified variants in 41% of CDH patients, respectively classified as pathogenic (2.5%), probably pathogenic (11%) and VUS (27.5%).
Conclusion: These results reinforce the need of genetic analysis in all CDH patients in order to identify new candidate genes related with the CDH pathophysiology.

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THE IMPACT OF THE PERINATAL CARE SETTING ON SURVIVAL AFTER FETOSCOPIC TRACHEAL OCCLUSION FOR SEVERE CONGENITAL DIAPHRAGMATIC HERNIA: A SYSTEMATIC REVIEW AND INDIVIDUAL PARTICIPANT ANALYSIS

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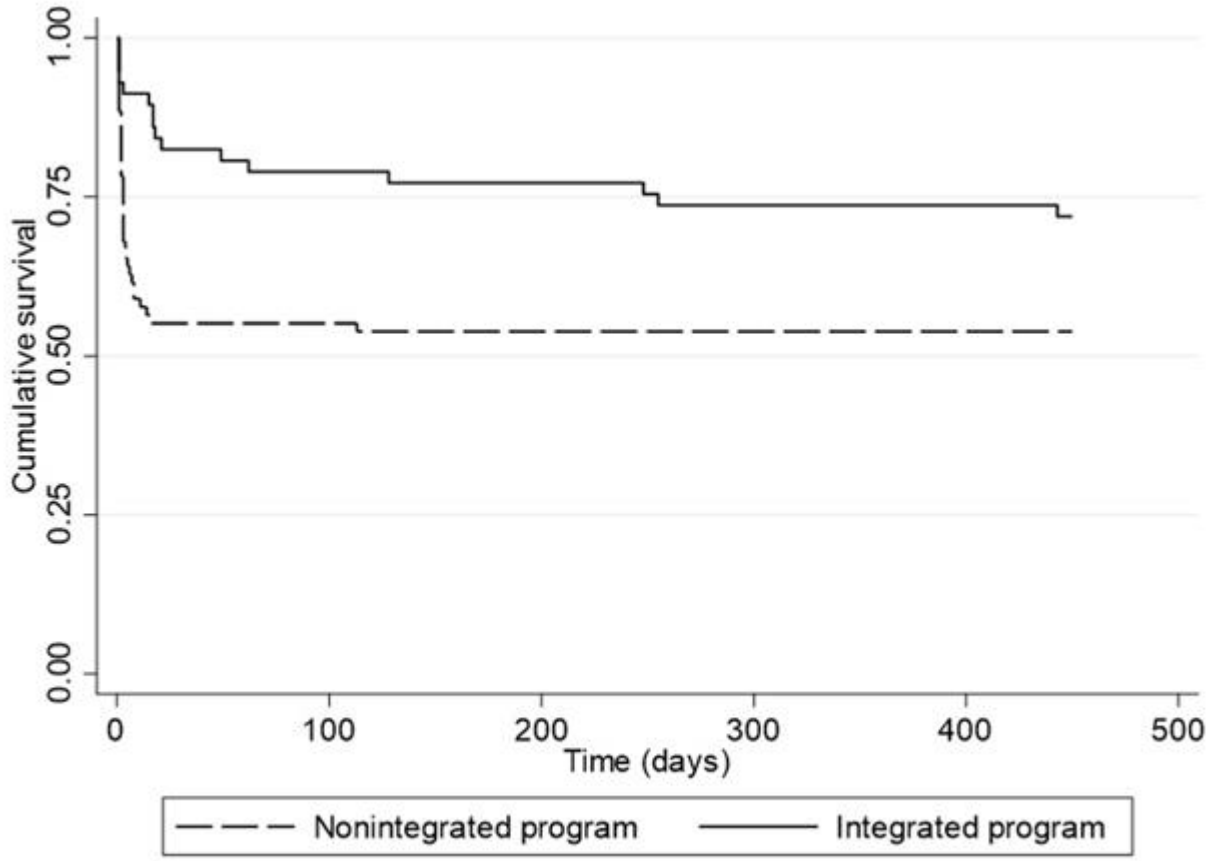
Background: Fetoscopic endoluminal tracheal occlusion (FETO) was recently shown to improve survival in severe congenital diaphragmatic hernia (CDH) in a multicenter, randomized trial. However, postnatal survival rates vary widely based on institutional care setting. In functional integrated centers, prenatal and postnatal CDH management occur at the same institution, while in others, delivery and postnatal management may occur at separate, nonintegrated institutions. We aimed to determine the survival rates after FETO in integrated vs. nonintegrated settings.

Methods: A systematic review (n=5 studies; 192 patients) and analysis of published individualized data (n=9 studies; 150 patients) was conducted from 2004-2021. The primary outcome was in-hospital survival following FETO, stratified by care setting. Statistical analyses were performed with forest plots, t-tests, Chi-squared, Kaplan-Meier estimates, and multilevel regression ($p \leq 0.05$).

Results: Patients in integrated care settings had significantly higher pre-FETO O/E LHR (25.6+/-5.8 vs. 23.3+/-7.3, p=0.04) compared to nonintegrated settings. However, there were comparable post-occlusion O/E LHR (51.9+/-25.3 vs. 49.1+/-23.2, p=0.57). Integrated programs had similar preterm prelabor rupture of membranes rates (44.8% vs. 38.1%, p=0.42), but delivered at later gestational ages (36.0+/-2.2 vs. 34.9+/-2.8 weeks, p=0.004). Patients in integrated settings showed significantly increased in-hospital survival rates (70.7% vs. 53.9%, p=0.003) and survived for longer (median survival 18 days vs. 2 days, p<0.001). Pooled results of the systematic review showed a significant survival benefit in FETO that was limited to the integrated cohort (OR 2.97; 95% CI 1.69-4.26). On multilevel logistic regression, access to ECMO (OR=18.8, p=0.049) significantly increased the odds of survival in both settings while controlling for markers of prenatal and postnatal severity.

Conclusions: Integrated programs with access to ECMO provide the highest survival rates for severe CDH patients undergoing FETO. This suggests that the effects of FETO and standardized postnatal management are complimentary and have the greatest impact when implemented at the same institution.

Images


Cumulative survival
0.00
0.25
0.50
0.75
1.00
0
100
200
300
400
500
Time (days)
Nonintegrated program
Integrated program

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Prenatal brain development is altered in Right Congenital Diaphragmatic Hernia on ultrasound

Dr Lennart Van Der Veeken[1], Dr Francesca Russo[1], Dr Ewelina Litwinska[2], Dr David Basurto[1], Dr Elisenda Eixarch[3], Prof Luc De Catte[1], Prof Kypros Nicolaides[2], Prof Jan Deprest[1]
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Objective
In left sided congenital diaphragmatic hernia (LCDH), recent studies suggests that brain development might already be altered prenatally. One potential mechanisms is that this is caused by a lower left cardiac output. In right sided CDH (RCDH), which is uncommon, brain growth has not yet been investigated in detail. In RCDH left cardiac output is most likely less affected. Therefore we aimed to determine body and brain size and brain perfusion in a cohort of RCDH fetuses.
Study design
This is a retrospective review of all fetuses with isolated RCDH that have been assessed in three referral centers (Barcelona, Leuven, London). We collected data on the abdominal circumference (AC), femur length (FL), biparietal diameter (BPD), head circumference (HC), transcerebellar diameter (TCD) and the Doppler waveform of the middle cerebral artery (MCA) during four gestational time periods: (<24w, 25-28w, 29-32w, >33w). We compared these to normative data and investigated the correlation with disease severity (observed/expected lung-to-head-ratio) and if fetoscopic endoluminal tracheal occlusion (FETO) affected brain or body size or MCA Doppler.
Results
Seventy-four fetuses were included in the analysis. The AC was within the normal range. Conversely, the HC was significantly larger in the third trimester, increasingly so with advancing gestational age. The TCD and ventricles were smaller in the third trimester. In 63% of fetuses the TCD was under the p5 and 47 % had a ventricular width below the p5. TCD correlated with disease severity. The MCA Doppler pulsatility index had a different evolution during the second trimester and third trimester compared to normal. FETO did not affect any of the measurements.
Conclusion
Fetuses with isolated RCDH have a smaller cerebellum in the third trimester. This correlated to disease severity. It is unlikely that a reduced left cardiac output is the underlying mechanism.

Graph

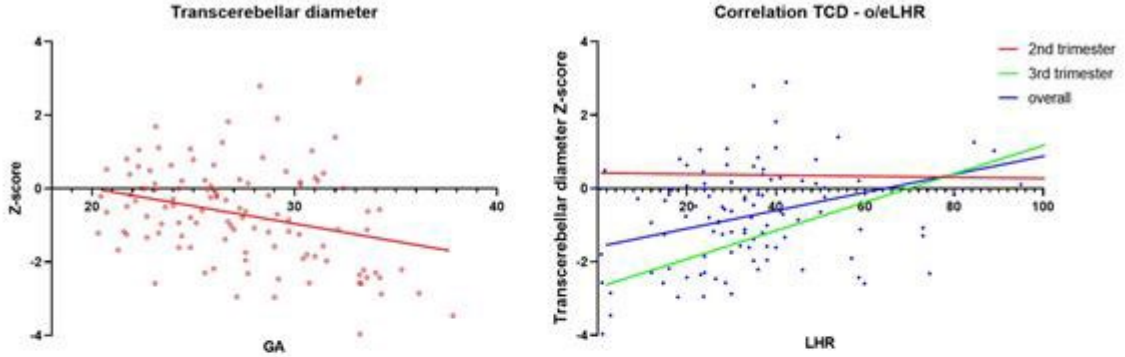

Figure 1: Left: Correlation and regression of the transcerebellar diameter Z-scores through gestation **Right**: correlation between the transcerebellar diameter and the observed/ expected lung-to-head ratio (o/e LHR) in the second (red) and third (green) trimester and overall (bleu).