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MATERNAL-FETAL MEDICINE

Application of the INTERGROWTH-21st chart compared to customized growth charts in fetuses with left heart obstruction: late trimester biometry, cerebroplacental hemodynamics and perinatal outcome

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Abstract

Purpose Birth weight (BW) is crucial for surgical outcome in children with left heart obstruction (LHO). Head circumference (HC) is believed to correlate with the neurocognitive outcome in LHO. Our aim was to investigate the application of international standardized growth charts from the INTERGROWTH-21st project in comparison to customized growth charts in fetal LHO.

Methods This is a retrospective cohort study consisting of 60 singleton pregnancies complicated by fetal LHO. For the *z* score calculation of estimated fetal weight (EFW) and biometric parameters, the INTERGROWTH-21st calculator was used as well as algorithms of customized growth charts. Antenatal measurements were compared to newborn biometry and the association with fetal Doppler results (MCA PI: middle cerebral artery pulsatility index and CPR: cerebroplacental ratio) was examined. Furthermore, the ability of each antenatal chart to predict adverse perinatal outcome was evaluated.

Results At a mean gestational age of 37 weeks, all assessment charts showed significantly smaller mean values for antenatal head circumference (HC) *z* scores. Highest detection rate for restricted HC growth antenatally was achieved with Hadlock charts. MCA PI and CPR were not associated with neonatal HC. A significant association was observed between EFW and 1-year survival, independent of the considered growth chart.

Conclusions Growth chart independently, antenatal HC did tend to be smaller in LHO fetuses. A significant association was observed between EFW and 1-year survival rate. Prospective investigations in CHD fetuses should be carried out with internationally standardized growth charts to better examine their prognostic value in this high-risk population.

Keywords Congenital heart disease · Left heart obstruction · Growth charts · Fetal biometry · Fetal hemodynamics

Introduction

Fetuses with congenital heart disease (CHD) often present with lower birth weight (BW) and head circumferences (HC) [1–3]. BW is an important predictor for survival outcomes of CHD, especially in children with single ventricle physiology like in hypoplastic left heart syndrome (HLHS) [4–7]. Fetuses with CHD are at high risk for poor neurodevelopmental outcome in later childhood [8–10]. HC at birth is associated with neurological outcome of CHD children [2, 11]. Different reports described significantly reduced HC in fetuses with CHD, which is assumed to be associated with altered cerebral hemodynamics [12–17] or other influences such as epigenetic or placental factors [18–20]. Own previous work demonstrated that, in particular, CHD

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fetuses with low placental blood content and, therefore, low oxygen delivery to the brain as in cases of severe left heart obstruction (LHO) show restricted HC growth throughout gestation depending on the direction of aortic arch flow and have altered cerebral hemodynamics in the third trimester of pregnancy [21, 22].

In general, research groups with focus on fetal biometry in CHD refer to own growth curves or use different reference algorithms for biometry calculation leading to a poor comparability. A multiethnic, population-related growth chart (INTERGROWTH-21st) has been recently established. The aim was to generate internationally standardized perinatal growth curves with potential usefulness in clinical interpretation of routinely taken ultrasound measurements. Furthermore, comparisons across populations should be improved [23, 24].

We hypothesized that the use of different biometry algorithms in CHD fetuses may have an impact on data heterogeneity. To our knowledge, INTERGROWTH-21st charts have not yet been used in studies on the biometry of CHD fetuses. In alignment with own previous results regarding head biometry and cerebroplacental hemodynamics in CHD, we further focused on the group with LHO. The aim of our study was to look for possible differences in the assessment of growth patterns when comparing INTERGROWTH-21st and customized growth charts in LHO.

Methods

A single-center cohort analysis was performed at the Department of Obstetrics and Gynecology, University Hospital rechts der Isar, and the Department of Pediatric Cardiology and Congenital Heart Defects, German Heart Centre Munich (Technical University of Munich). We retrospectively included all pregnant women with the suspicion of fetal LHO at the routine scan being referred to our prenatal diagnosis unit from March 2008 to March 2018. In our unit, in case of CHD, fetal echocardiography was performed interdisciplinary by an obstetrician and a pediatric cardiologist. Genetic testing was discussed with the parents to rule out associated chromosomal or genetic disorders. All neonates underwent postnatal echocardiography to ascertain prenatal diagnosis of CHD. In the case of termination of pregnancy, autopsy was done in accordance with parents' request.

All patient information was retrieved from clinical files or from ViewPoint® database. Perinatal outcome data included 5-min APGAR, pH value and base excess (umbilical artery), 30-day survival rate and 1-year survival rate. LHO included hypoplastic left heart (HLH) with hypoplastic left heart syndrome or hypoplastic left heart complex and aortic arch obstruction (AAO) with hypoplastic/interrupted aortic arch or isolated aortic coarctation, based on the modified CHD categorization by Haveman et al. [19, 25]. Functional cardiac abnormalities such as arrhythmias, extracardiac abnormalities, chromosomal abnormalities including syndromic disorders with possible influence on fetal growth were excluded. Furthermore, cases with significant placental insufficiency and maternal diseases such as preeclampsia or diabetes as well as cases with maternal smoking were also excluded from analysis. Repeated measurements with assessment of fetal wellbeing using biometry and fetal Doppler as well as re-examination of LHO were performed routinely in early and late third trimester. Gestational age (GA) was defined based on the first day of the last menstrual period and confirmed by crown-rump length measurement at the first-trimester ultrasound scan. Fetal biometry routinely included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). Estimated fetal weight (EFW) was calculated using the Hadlock formula [26]. For statistical analysis, the last measurement of fetal biometry and Doppler was used. Fetal echocardiography was performed according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [27]. Doppler recordings (UA PI: umbilical artery pulsatility index, MCA PI: middle cerebral artery PI) were performed as previously described [28]. UA PI was defined as normal when it was < 95th centile for gestational age [29]. MCA PI was defined as abnormal when it was < 5th centile [25]. Cerebroplacental ratio (CPR) was calculated as the ratio of MCA PI to UA PI, and considered abnormal when < 5th centile [30]. Ultrasound systems used were Voluson E 8 or Voluson 730 Expert GE Medical Systems, Munich, Germany.

To assess EFW and biometry components (BPD, HC, AC, FL) antenatally on the one hand, centile and z scores were calculated using established biometric algorithms from Snijders and Nicolaides [31] and Hadlock et al. [26, 32] as well as Marsal et al. [33]. Centiles and z scores for newborn BW and postnatal occipitofrontal circumference (OFC) were calculated by established biometric algorithms from Voigt et al. [34] and Nicolaides et al. [35]. On the other hand we used new biometric algorithms from INTERGROWTH-21st (IG-21st) for pre- and postnatal weight and biometry components [23, 24].

Statistical analysis

For quantitative data, means and standard deviations are presented, for categorical data absolute and relative frequencies are shown. Means of z score values of biometric parameters in LHO fetuses were compared to a value of zero, which would be expected for a healthy reference population. For comparison of mean z scores between different charts repeated measurement ANOVA was performed.

Charts were also compared with regard to frequencies of detected microcephaly, defined as HC or OFC < 3rd centile, and small for gestational age (SGA), defined as EFW or BW < 10th centile. For comparison of two charts, McNemar's test was performed. Cochran's *Q* test was used to compare dependent categorical data between three charts.

Possible association of delayed growth patterns to fetal Doppler measurements was assessed. Furthermore, analyzed data were collected in terms of sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR−) for each antenatal assessment tool in relation to each postnatal BW and OFC assessment tool. Finally, prognostic value of the different antenatal assessment tools for the prediction of perinatal outcome and survival was analyzed using the area under the receiver operating characteristic (ROC) curve (AUC). Differences between AUCs were assessed using DeLong's test. All statistical tests were conducted two sided and a p value < 0.05 was considered statistically significant. For relevant quantities, 95% confidence intervals (95% CI) are presented. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) and R version 3.3.4 (The R Foundation for Statistical Computing).

Ethical approval

The local Institutional Ethic Board (Ethikkommission der Fakultät für Medizin der Technischen Universität München) approved the study (protocol number 157/18). The study was not registered in a public trial registry.

Results

Baseline characteristics of the LHO cohort and data on perinatal outcome

During the study period, 109 pregnancies complicated by fetal LHO could be detected with 60 pregnancies meeting inclusion criteria. Baseline characteristics of the study cohort and data on pregnancy outcome are shown in Table 1. Out of the 60 included pregnancies, 38 children were diagnosed with HLH and 22 patients with AAO. Mean GA at delivery was 38 ± 2 weeks. 5-min APGAR was smaller or even to 7 in 13 (31.6%) HLH infants compared to one patient (4.5%) with AAO ($p = 0.024$). Mortality was higher in HLH as compared to AAO patients (one year: 35.1% vs 5.9%, $p = 0.004$; 30 days: 23.6% vs 4.8%, $p = 0.076$). Based on these findings and the known higher mortality rate for HLH compared to AAO children, we focused survival analyses solely on HLH patients. Here, 30-day mortality data were available for 38 HLH (100.0%) and one-year mortality data were available for 37 HLH (97.4%) cases, respectively.

Comparison of LHO growth patterns to normal population antenatally

In Table 2, mean z scores (with standard deviations, minima and maxima) and centiles for each antenatal parameter using the different growth charts are provided. When assessing growth charts from Snijder and Nicolaides and Hadlock et al., mean z values were found to be significantly smaller than zero (the mean value that would be expected in a healthy population) for all biometric parameters (BPD, HC, AC, FL). For HC, z score (zHC) calculated with IG-21st showed also significant smaller values compared to normal population ($z\text{HC} = -0.32 \pm 1.16$, $p = 0.036$). However, for all other biometric parameters, when assessed with INTERGROWTH-21st, mean values were either negative but not significantly different from zero ($z\text{BPD} = -0.08 \pm 1.12$, $p = 0.559$; $z\text{AC} = -0.06 \pm 0.87$, $p = 0.571$; respectively) or positive and not significantly different from zero ($z\text{FL} = 0.25 \pm 1.09$, $p = 0.243$). For EFW calculated with Marsal et al. a significantly smaller z value was observed in LHO fetuses compared to normal population ($z\text{EFW} = -0.45 \pm 0.94$, $p < 0.001$). This was not observed for EFW calculated by IG-21st ($z\text{EFW} = 0.11 \pm 0.87$, $p = 0.346$).

Comparison of growth charts detecting delayed growth in LHO

For calculation of EFW the diagnosis SGA could be found in three fetuses (5.0%) using IG-21st and in four fetuses (6.6%) using the Marsal chart ($p = 1.000$, Table 3). Microcephaly was diagnosed in 14 fetuses (25.0%) using the Hadlock chart compared to 3 fetuses (5.0%) with Snijder chart as well as 5 fetuses (8.3%) using the IG-21st chart ($p < 0.001$, Table 3).

When using the three different birth charts, the diagnosis SGA could be found in seven patients (12%) using Voigt chart as well as Nicolaides chart and in four patients (7%) using the IG-21st chart ($p = 0.115$, Table 4). Microcephaly was diagnosed in seven children (14%) using the Voigt chart and in one child (5%) using the IG-21st chart ($p = 0.031$, Table 4).

Prediction of postnatal SGA and microcephaly in LHO fetuses using antenatal charts

The predictive value of the antenatal charts for postnatal SGA and microcephaly was assessed and results are shown in Tables 1 and 2 (supplementary material). EFW and AC were compared against BW charts (Table 1, supplementary material). Here, highest sensitivity of 75% was found when comparing AC-Hadlock against the IG-21st BW chart. Moreover, AC-Hadlock had the highest sensitivities of 50–75% throughout all comparisons. Overall

Table 1 Baseline characteristics of maternal data and perinatal outcome in fetuses with left heart obstruction

	Total ($n=60$)	HLH ($n=38$)	AAO ($n=22$)	p value
Maternal characteristics				
Maternal age (years), mean ± SD	31 ± 5	31 ± 5	32 ± 6	0.432
Nullipara, *n* (%)	33 (55.0%)[a]	18 (47.4%)[b]	12 (54.5%)[c]	0.490
Positive family medical history, *n* (%)	7 (11.7%)[a]	2 (5.2%)[b]	5 (22.7%)[c]	0.039*
International patients, *n* (%)	15 (25.0%)[a]	9 (23.7%)[b]	6 (27.3%)[c]	0.151
GA at last examination (weeks), mean ± SD	37 ± 3	37 ± 3	37 ± 3	0.580
Fetal characteristics				
Antenatal EFW (g), mean ± SD	2887 ± 616	2834 ± 559	2980 ± 707	0.481
Antenatal HC (mm), mean ± SD	316.2 ± 35.1	318.4 ± 23.3	312.6 ± 49.9	0.569
Antenatal BPD (mm), mean ± SD	91.6 ± 6.3	91.0 ± 6.6	92.7 ± 5.7	0.340
Antenatal AC (mm), mean ± SD	322.4 ± 29.8	321.2 ± 27.3	324.5 ± 34.3	0.444
Antenatal FL (mm), mean ± SD	68.7 ± 6.0	68.0 ± 6.1	70.0 ± 5.6	0.227
Foramen ovale restriction, *n* (%)	7 (11.7%)[a]	7 (18.4%)[b]	0 (0.0%)[c]	0.040*
Reverse aortic arch flow, *n* (%)	40 (66.7%)	32 (84.2%)	8 (36.4%)	0.001*
Spontaneous vaginal delivery, *n* (%)	29 (48.3%)[a]	20 (52.6%)[b]	9 (40.9%)[c]	0.494
Neonatal outcome				
GA at birth (weeks), mean ± SD	38 ± 2	38 ± 1	39 ± 2	0.539
Male infant, *n* (%)	42 (70.0%)[a]	30 (78.9%)[b]	12 (54.5%)[c]	0.078
Birth < 37 weeks' GA, *n* (%)	3 (5.0%)[a]	2 (5.2%)[b]	1 (4.5%)[c]	1.000
Birth weight (g), mean ± SD	3078 ± 515	3057 ± 467	3114 ± 598	0.411
Low birth weight < 2500 g, *n* (%)	6 (10.0%)	3 (7.9%)	3 (13.6%)	0.659
OFC (cm), mean ± SD	33.6 ± 1.7	33.7 ± 1.8	33.4 ± 1.6	0.419
APGAR 5 ≤ 7, *n* (%)	13 (21.6%)[a]	12 (31.6%)[b]	1 (4.5%)[c]	0.024*
Umbilical artery pH, mean ± SD	7.27 ± 0.08	7.27 ± 0.08	7.28 ± 0.07	0.596
Umbilical artery base excess, mean ± SD	− 4.8 ± 3.3	− 5.4 ± 3.7	− 3.6 ± 2.2	0.589
pO_2 pressure (mmHg), mean ± SD	33.9 ± 8.3	33.0 ± 5.5	35.5 ± 12.0	0.263
Cardiac catheterization < 48 h, *n* (%)	2 (3.3%)[a]	2 (5.2%)[b]	0 (0%)[c]	0.469
Catecholamines < 48 h, *n* (%)	3 (5.0%)[a]	3 (7.9%)[b]	0 (0%)c	0.018*
Resuscitation < 48 h, *n* (%)	1 (1.6%)[a]	1 (2.6%)[b]	0 (0%)[c]	0.414
Neonatal death (< 30 days), *n* (%)	10 (16.9%)[d]	9 (23.6%)[e]	1 (4.8%)[f]	0.076
Mortality within 12 months, *n* (%)	14 (25.9%)[d]	13 (35.1%)[e]	1 (5.9%)[f]	0.004*

Data are given as mean (*n*) ± standard deviation (SD) for quantitative data. Categorical data were compared using the Chi-square test. Bivariate relationship of quantitative data was assessed by the Fisher's exact test. Subgroups were generated with *AAO* aortic arch obstruction, *HLH* hypoplastic left heart, *EFW* estimated fetal weight, *SGA* small for gestational age, *HC* head circumference, *BPD* biparietal diameter, *AC* abdominal circumference, *FL* femur length

*A p value < 0.05 was considered statistically significant

[a]Percentage out of 60 pregnancies

[b]Percentage out of 38 pregnancies

[c]Percentage out of 22 pregnancies

[d]Percentage out of 59 recorded events within first 30 days and out of 54 within 12 months

[e]Percentage out of 38 recorded events within first 30 days and out of 37 within 12 months

[f]Percentage out of 21 recorded events within first 30 days and out of 17 within 12 months

specificities ranged from 90 to 100%. When comparing HC against OFC (Table 2, supplementary material), the highest sensitivity of 33% was found for antenatal Hadlock chart when compared against the Voigt chart for newborn biometry. Here, specificities ranged from 75 to 95%.

Table 2 Mean *z* scores and centiles of the antenatal size assessment tools for biometric parameters

Antenatal size assessment tools: overview														
	BPD-Hadlock (*z* score)	BPD-Snijder (*z* score)	BPD-IG-21st (*z* score)	HC-Hadlock (*z* score)	HC-Snijder (*z* score)	HC-IG-21st (*z* score)	AC-Hadlock (*z* score)	AC-Snijder (*z* score)	AC-IG-21st (*z* score)	FL-Hadlock (*z* score)	FL-Snijder (*z* score)	FL-IG-21st (*z* score)	EFW-Marsal (*z* score)	EFW-IG-21st (*z* score)
Antenatal parameters (*z* score)														
N	56	60	60	56	60	60	56	60	60	56	60	60	60	60
Mean	0.56	− 0.41	− 0.08	− 1.35	− 0.48	− 0.32	− 0.35	− 0.24	− 0.06	− 1.35	− 0.39	0.25	− 0.45	0.11
p value	0.001*	0.002*	0.559	< 0.001*	< 0.001*	0.036*	0.024*	0.018*	0.571	< 0.001*	0.006*	0.243	< 0.001*	0.346
SD	1.25	.96	1.12	1.37	.93	1.16	1.12	.78	.87	1.09	1.07	1.09	.94	.87
Minimum	− 2	− 2.33	− 2.21	− 4	− 3.72	− 3.72	− 4	− 3.72	− 3.24	− 4	− 3.72	− 2.97	− 3.72	− 2.70
Maximum	4	3.72	3.72	1	1.23	1.83	3	1.48	1.96	1	1.41	2.32	2.05	2.35
Antenatal parameters (centile)														
N	56	60	60	56	60	60	56	60	60	56	60	60	60	60
Mean	64	37	47	22	37	43	41	43	49	18	41	59	37	54
p value	0.002*	<0.001*	0.379	<0.001*	<0.001*	0.068	0.013*	0.014*	0.734	<0.001*	0.015*	0.023*	<0.001*	0.241
SD	32	26	30	25	25	31	27	21	23	17	27	29	24	24
Minimum	1	1	1	0	0	0	0	0	0	0	0	0	0	0
Maximum	100	100	97	87	89	97	100	93	97	71	92	99	98	99

p values were calculated using one sample *t* test

BPD biparietal diameter, *HC* head circumference, *AC* abdominal circumference, *FL* femur length, *EFW* estimated fetal weight

*A *p* value < 0.05 was considered statistically significant

Table 3 Comparison of the different antenatal charts with regard on restricted growth parameters

Fetal measurements	Hadlock ($n=56$)	Snijder ($n=60$)	IG-21st ($n=60$)	Marsal ($n=60$)	P value*
EFW z score, mean ± SD	na	na	0.11 ± 0.94	− 0.45 ± 0.94	< 0.001[a]
HC z score, mean ± SD	− 1.35 ± 1.37	− 0.48 ± 0.93	− 0.32 ± 1.16	na	< 0.001[d]
BPD z score, mean ± SD	0.56 ± 1.25	− 0.41 ± 0.96	− 0.08 ± 1.12	na	< 0.001[d]
AC z score, mean ± SD	− 0.35 ± 1.12	− 0.24 ± 0.78	− 0.06 ± 0.87	na	< 0.001[d]
FL z score, mean ± SD	− 1.35 ± 1.09	− 0.39 ± 1.07	0.25 ± 1.09	na	< 0.001[d]
SGA, *n* (%)	na	na	3 (5.0%)	4 (6.6%)	1.000[b]
Microcephaly, *n* (%)	14 (25.0%)	3 (5.0%)	5 (8.3%)	na	< 0.001[c]
Small head, *n* (%)	27 (48.2%)	12 (20.0%)	12 (20.0%)	na	< 0.001[c]
AC < 3rd centile, *n* (%)	3 (5.3%)	2 (3.3%)	3 (5.0%)	na	0.368[c]
AC < 10th centile, *n* (%)	7 (12.5%)	3 (5.0%)	3 (5.0%)	na	0.018[c]
FL < 5th centile, *n* (%)	17 (30.3%)	5 (8.3%)	3 (5.0%)	na	0.001[c]

Data are given either as absolute number (*n*) and percentage of total patients (for each chart) or as mean ± standard deviation (SD) for quantitative data

IG-21st INTERGROWTH-21st, *EFW* estimated fetal weight, *SGA* small for gestational age (EFW < 10th centile), *HC* head circumference, *BPD* biparietal diameter, *AC* abdominal circumference, *FL* femur length, *microcephaly* HC < 3rd centile, *small head* HC < 10th centile), *na* not applicable

*A p value < 0.05 was considered statistically significant

[a]Comparison using paired t test

[b]Comparison using McNemar's test

[c]Comparison using Cochran's Q test

[d]Comparison using ANOVA

Table 4 Comparison of the different postnatal charts with regard on restricted growth parameters

Newborn measurements	Voigt BW: $n=60$ OFC: $n=58$	IG-21st BW: $n=60$ OFC: $n=58$	Nicolaides BW: $n=60$ OFC: $n=58$	p value*
SGA, *n* (%)	7 (11.7%)	4 (6.7%)	8 (13.3%)	0.115[a]
Microcephaly, *n* (%)	7 (12.1%)	1 (1.7%)	na	0.031[b]
Small head, *n* (%)	15 (25.9%)	6 (10.3%)	na	0.004[b]

Data are given as absolute number (*n*) and percentage of total patients (for each chart)

IG-21st INTERGROWTH-21st, *BW* birth weight, *SGA* small for gestational age (BW < 10th centile), *OFC* occipitofrontal circumference, *microcephaly* OFC < 3rd centile, *small head* OFC < 10th centile, *na* not applicable

*A p value < 0.05 was considered statistically significant

[a]Comparison using Cochran's Q test

[b]Comparison using McNemar's test

Table 5 Comparison of fetal Doppler measurements with regard on fetal head size

Fetal Doppler	Normal head (Hadlock)	Small head (Hadlock)	Microcephaly (Hadlock)	Reverse aortic arch flow ($n=43$)	p value*
UA PI, mean ± SD	0.98 ± 0.18	0.99 ± 0.13	0.98 ± 0.15	0.98 ± 0.16	0.978[a]
MCA PI, mean ± SD	1.43 ± 0.25	1.49 ± 0.41	1.50 ± 0.43	1.46 ± 0.35	0.777[a]
CPR, mean ± SD	1.45 ± 0.36	1.55 ± 0.48	1.57 ± 0.46	1.55 ± 0.46	0.781[a]

Data are given as mean ± standard deviation (SD)

UA PI umbilical artery pulsatility index, *MCA PI* middle cerebral artery pulsatility index, *CPR* cerebroplacental ratio, *Normal head* HC ≥ 10th centile, *small head* HC < 10th centile, *microcephaly* HC < 3th centile

*A p value < 0.05 was considered statistically significant

[a]Comparison using ANOVA

Fetal cerebral hemodynamics and its association to head biometry in LHO

Due to their highest detection rate regarding small head biometry, the Hadlock chart (antenatally) and the Voigt chart (postnatally) were used for the analysis of cerebral blood flow association. A subset of LHO fetuses had Doppler examinations including UA PI and MCA PI as well as CPR at final measurement (Tables 5, 6). MCA PI was abnormal (< 5th centile) in seven LHO fetuses (16.3%) with normal head size (> 10 centile) compared to two LHO fetuses (13.3%) with small head size at birth as well as one LHO fetus (14.2%) with microcephaly postnatally ($p = 0.844$, Table 5). Mean MCA PI was 1.43 ± 0.25 in fetuses with normal head growth and 1.49 ± 0.41 in fetuses with small head size as well as 1.50 ± 0.43 in LHO fetuses with microcephaly antenatally ($p = 0.777$, Table 5). Notably, UA Doppler analysis was normal (< 95th centile) for all LHO fetuses, suggesting that there were no cases with severe placental insufficiency. CPR was abnormal in six LHO fetuses (14.0%) with normal head size (> 10 centile) compared to four LHO fetuses (26.7%) with small head size at birth as well as five LHO fetuses (42.9%) with microcephaly postnatally ($p = 0.178$, Table 6). The mean CPR was 1.45 ± 0.36 in fetuses with normal growth and 1.55 ± 0.48 in fetuses with small head biometry as well as 1.57 ± 0.46 in LHO fetuses with microcephaly antenatally ($p = 0.781$, Table 6).

Antenatal prediction of adverse perinatal outcome and survival in LHO

As postnatal resuscitation and umbilical artery pH < 7.1 occurred only in one patient and base excess < − 12 mmol/l was not found in any newborn, we excluded these parameters for analysis. As mentioned above due to significant higher mortality rate for HLH compared to AAO children, we restricted survival analysis solely to HLH patients.

ROC analysis revealed no significant association between any of the antenatal size assessment tools regarding 5-min APGAR and neonatal death < 30 days (Table 7). For the outcome death within the first year, a significant association could be found for both EFW charts (EFW-Marsal: AUC = 0.754, $p = 0.013$, 95% CI 0.58–0.91; EFW-IG-21st: AUC = 0.756, $p = 0.013$, 95% CI 0.58–0.93) (Fig. 1). For these scenarios, DeLong's test for two correlated ROC curves demonstrated no significant difference among EFW-Marsal and EFW-IG-21st ($p = 0.655$) as well as FL-Snijder and FL-IG-21st ($p = 0.505$). However, curves for FL-Hadlock and FL-IG-21st plotted against death within the first year differed significantly ($p = 0.049$).

Furthermore, FL was plotted against death within the first year including only patients without a prenatal SGA diagnosis (SGA defined as EFW Marsal < 10th centile) (Fig. 2). Here, all three growth charts showed a significant association with 1-year mortality (FL-Hadlock, non-SGA:

Table 6 Comparison of abnormal fetal Doppler measurements with regard on postnatal head size charts

Fetal Doppler	Prenatal detection	Normal heads[a] ($n = 43$)	Small heads[b] ($n = 15$)	Microcephaly[c] ($n = 7$)	p value*	Normal heads[a] + reverse aortic arch flow ($n = 32$)	Small heads[b] + reverse aortic arch flow ($n = 6$)	Microcephaly[c] + reverse aortic arch flow ($n = 3$)	p value*
UA PI > 95th centile, *n* (%)	0 (0.0%)[d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	na	0 (0.0%)	0 (0.0%)	0 (0.0%)	na
MCA PI < 5th centile, *n* (%)	9 (16.1%)[e]	7 (16.3%)	2 (13.3%)	1 (14.2%)	0.844[g]	4 (12.5%)	0 (0.0%)	0 (0.0%)	0.500[g]
CPR < 5th centile, *n* (%)	10 (19.2%)[f]	6 (14.0%)	4 (26.7%)	3 (42.9%)	0.178[g]	4 (12.5%)	2 (33.3%)	1 (33.3%)	0.500[g]

Data are given as absolute number (n) and percentage of total patients (for each chart)

IG-21st INTERGROWTH-21st, *HC* head circumference, *OFC* occipitofrontal circumference, *UA PI* umbilical artery pulsatility index, *MCA PI* middle cerebral artery pulsatility index, *CPR* cerebroplacental ratio, *na* not applicable

*A p value < 0.05 was considered statistically significant

[a]Normal heads: OFC-Voigt ≥ 10th centile

[b]Small heads: OFC-Voigt < 10th centile

[c]Microcephaly: OFC-Voigt < 3rd centile

[d]Percentage out of 54 Doppler measurements

[e]Percentage out of 56 Doppler measurements

[f]Percentage out of 52 Doppler measurements

[g]Comparison using ANOVA

Table 7 Area under the curve (AUC) of ROC curves for antenatal prediction of adverse outcome

Antenatal size assessment tool	Area under the curve (AUC)	Asymptotic significance	95% confidence interval	
			Lower bound	Upper bound
Neonatal death				
BPD-Hadlock	0.587	0.392	0.405	0.769
BPD-Snijder	0.549	0.630	0.353	0.745
BPD-IG-21st	0.591	0.369	0.404	0.779
HC-Hadlock	0.584	0.410	0.381	0.786
HC-Snijder	0.582	0.422	0.377	0.786
HC-IG-21st	0.593	0.358	0.388	0.799
AC-Hadlock	0.567	0.507	0.351	0.783
AC-Snijder	0.550	0.623	0.325	0.775
AC-IG-21st	0.539	0.700	0.311	0.768
FL-Hadlock	0.564	0.528	0.375	0.754
FL-Snijder	0.599	0.330	0.407	0.791
FL-IG-21st	0.611	0.275	0.420	0.802
EFW-Marsal	0.663	0.109	0.466	0.860
EFW-IG-21st	0.661	0.113	0.465	0.857
Death < 1 year				
BPD-Hadlock	0.594	0.298	0.429	0.758
BPD-Snijder	0.565	0.466	0.397	0.734
BPD-IG-21st	0.594	0.298	0.430	0.757
HC-Hadlock	0.589	0.321	0.420	0.759
HC-Snijder	0.590	0.316	0.423	0.757
HC-IG-21st	0.592	0.307	0.422	0.762
AC-Hadlock	0.575	0.405	0.392	0.758
AC-Snijder	0.557	0.526	0.366	0.748
AC-IG-21st	0.561	0.496	0.373	0.749
FL-Hadlock	0.650	0.096	0.483	0.817
FL-Snijder	0.676	0.050	0.513	0.839
FL-IG-21st	0.685	0.039*	0.523	0.847
EFW-Marsal	0.703	0.024*	0.545	0.861
EFW-IG-21st	0.697	0.028*	0.540	0.855
FL-Hadlock, non-SGA[a]	0.700	0.032*	0.529	0.872
FL-Snijder, non-SGA[a]	0.718	0.020*	0.546	0.890
FL-IG-21st, non-SGA[a]	0.728	0.015*	0.558	0.898

IG-21st INTERGROWTH-21st, *BPD* biparietal diameter, *HC* head circumference, *AC* abdominal circumference, *FL* femur length, *EFW* estimated fetal weight, *SGA* small for gestational age

*A p value < 0.05 was considered statistically significant

[a]Non-SGA = EFW Marsal > 10th centile

AUC = 0.700, $p = 0.032$, 95% CI 0.529–0.872; FL-Snijder, non-SGA: AUC = 0.718, $p = 0.020$, 95% CI 0.546–0.890; FL-IG-21st, non-SGA: AUC = 0.728, $p = 0.015$, 95% CI 0.558–0.898). In non-SGA patients, DeLong's test for two correlated ROC curves demonstrated no significant difference among FL-Hadlock, FL-Snijder and FL-IG-21st ($p = 0.071$–0.492).

Discussion

This study shows that first, consistent with previous studies [2, 16, 36–38], children with LHO present postnatally with higher rates of smaller OFC and lower BW. By definition, in a normal population, we would expect 10% of all newborns to be SGA and 3% showing microcephaly. Therefore, in our cohort, all three newborn size charts showed an increased incidence of microcephaly postnatally. In contrast, for SGA only when using Nicolaides and Voigt charts, we observed higher percentages of SGA compared to a normal

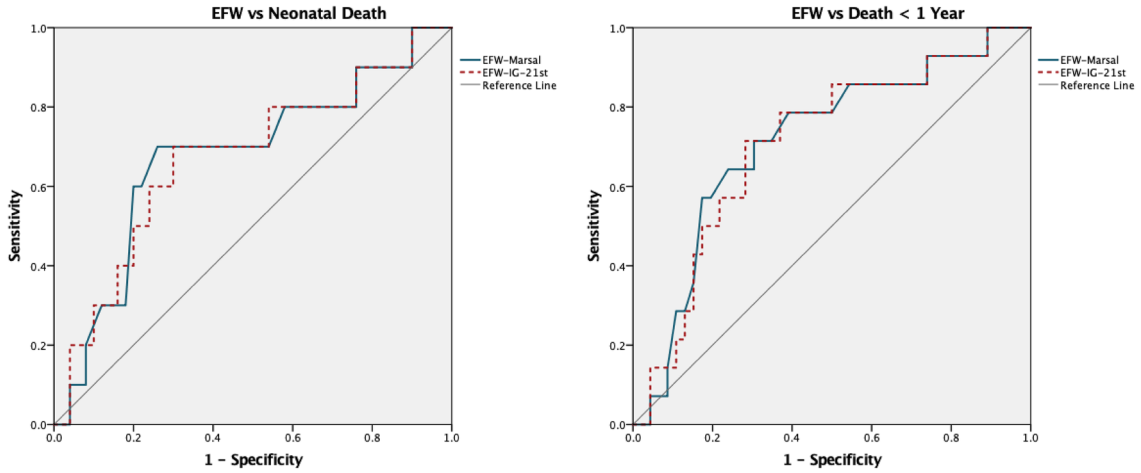

Fig. 1 Receiver operating characteristic (ROC) curves for EFW charts plotted against neonatal death and death < 1 year. *EFW* estimated fetal weight, *IG-21st* INTERGROWTH-21st

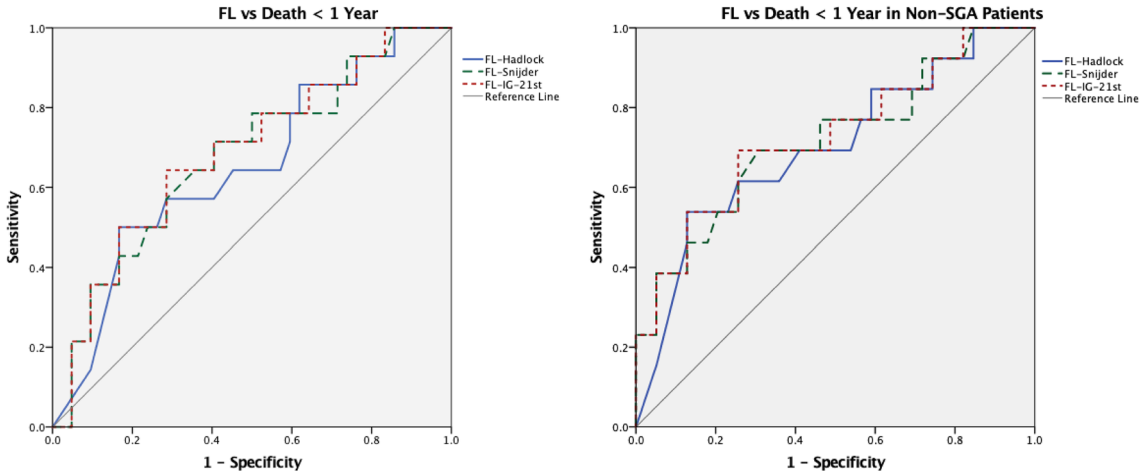

Fig. 2 Receiver operating characteristic (ROC) curves for FL charts plotted against death < 1 year when all patients (left) and when only patients without SGA diagnosis (EFW Marsal > 10th centile) (right) are included. *FL* femur length, *IG-21st* INTERGROWTH-21st

population. It has been known for some time that CHD children are significantly smaller than normal population [1, 39]. In our cohort, 12% of the LHO fetuses had a BW below the 10th percentile using established customized growth charts, which is similar to the 17–18% reported for CHD in general by Mathiessen et al. and Haveman et al. [2, 19]. This may indicate that a smaller HC is antenatally and postnatally associated with generally limited growth. In HLHS, however, even after adaptation of HC to the low BW, a significant deviation from normal population was reported [37, 38]. In our cohort, microcephaly was diagnosed in 12% of LHO newborns using customized growth charts, which is the same as previous results of Hangge et al. who reported an incidence of 12% for HLHS neonates [11]. Here, INTERGROWTH-21st charts showed for both parameters (OFC and BW) the lowest percentages of microcephaly (2%) and SGA (7%). When assessing fetal biometry antenatally, IG-21st differs from the other charts as well by generally estimating higher centiles and *z* scores for LHO fetuses compared to Hadlock charts.

Second, we observed significant lower *z* scores for all HC charts in LHO fetuses compared to normal population. The counselling of parents antenatally regarding neurodevelopmental outcome in CHD fetuses is frequently discussed [40], as a high percentage of CHD children are reported to have neurological abnormalities even before postnatal surgery [41]. Masoller et al. described smaller BPD and HC in CHD fetuses regardless of the type of CHD anomaly [13, 14]. However, other authors reported restricted head biometry in HLHS fetuses or CHD that are associated with impaired

cerebral oxygen saturation [15, 17]. Own work revealed that CHD fetuses in general do not have significantly smaller HC. This was only observed in fetuses with LHO, where HC becomes smaller in cases with retrograde aortic arch flow [21].

Changes in cerebroplacental hemodynamics of LHO fetuses may have an influence on HC growth restriction and neurodevelopmental abnormalities; however, there is no clear evidence. In a systematic review, Mebius and colleagues reported 22 studies on cerebral Doppler examinations in CHD fetuses compared to normal population. A lower MCA PI was described in 86% and a lower CPR in 75% of reported articles. Similar to the "brain sparing" effect in placental insufficiency reflecting fetal hypoxia, fetuses with HLHS or CHD, in which impaired cerebral oxygen saturation occurs, had a lower MCA PI compared to controls [3]. Yamamoto et al. described a significantly positive correlation between MCA PI and neonatal HC in a small cohort of HLHS with reversed aortic arch flow [16]. In our study, third, we could not detect a significant association between small head biometry and signs of cerebral redistribution antenatally reflected by pathological MCA PI and CPR. This is in line with Hangge et al., who reported no significant association between cerebral blood flow impedance and restricted head growth in HLHS postnatally [11]. Mebius et al. hypothesized that other mechanisms than fetal circulatory patterns may influence cerebral development. They found that fetal head growth neither is associated with cerebral blood flow patterns nor is influenced by the cerebral arterial oxygen saturation [20].

For the antenatal prediction of lower BW and HC in LHO children, sensitivities, specificities and likelihood ratios were comparable between the different biometry algorithm tools. As described before, microcephaly and SGA are slightly more often in LHO newborns than in an average population, which is also depicted by the general antenatal trends, especially regarding HC. However, a wide variation in the diagnostic accuracy of various antenatal tools for the prediction of both SGA and microcephaly has been described before [42, 43].

Growth chart independently, we observed a significant association between EFW and 1-year survival rate in HLH fetuses. In general, our mortality rates for HLH patients seem to be slightly higher compared to published results [44], which could be influenced by the higher rate of cases (18%) with severely restrictive foramen ovale or intact interatrial septum in our cohort as they are known to increase perinatal mortality rates significantly [45, 46]. Hangge et al. reported no increased 1-year mortality in HLHS infants with low birth weight (< 2500 g) or SGA [11], which is in contrast to earlier studies describing weight-related 1-year mortality after surgery [47, 48]. Neither did they observe an association of small head size and 1-year mortality [1]. Our results suggest that EFW could be an indicator for 1-year survival, independent from which growth chart is used for assessment. Furthermore, our data suggest that in patients, who have an EFW appropriate for gestational age, FL may be used as predictor for 1-year mortality, again growth chart independently. The predictive value of isolated short fetal femur lengths in terms of adverse outcome in prenatally healthy cohorts has been a focus of several recent studies [49–52]. D'Ambrosio et al. reported a significant association between short FL and fetal mortality as well as poor perinatal outcome [49]. Goetzinger et al. proposed that a short FL may be a sign of an adaptive response to chronic hypoxia [53].

There are several limitations to our study. First, our LHO cases were collected retrospectively. Furthermore, as the prevalence of severe congenital LHO is small, only 60 pregnancies fulfilled our inclusion criteria during the last 10 years. Consequently, the study is not powered to detect small differences between groups or growth charts. Although our work shows clear trends using fetal biometric parameters as prognostic and predictive markers in LHO patients, it must be noted that most likely due to relatively low case numbers of SGA and microcephaly, postnatally sensitivities and specificities are insufficient for binding counselling. Hence, to validate our findings, further investigations presumably in a multi-centric setting should be carried out to generate higher detection rates and valid guidelines for counselling parents. As we did not determine neurodevelopmental outcome of LHO fetuses, no association between HC growth and neurodevelopmental impairment could be identified. In regard to BPD, it must also be noted that Hadlock et al. established their growth curves measuring the diameter from one outer border of the parietal bone to the inner boarder of the other side (outer to inner) [54] whereas IG-21st used the diameter between both outer borders of the parietal bones (outer to outer) [23]. As this could already lead to varying results when evaluating and comparing different growth charts, we focused mainly on HC as the parameter for head growth.

In conclusion, antenatal HC did tend to be smaller in LHO fetuses growth chart independently. Highest detection rate for restricted HC growth antenatally was achieved with Hadlock charts. Cerebral redistribution was not associated with restricted head growth. Using all growth charts, a significant association was observed between EFW and 1-year survival rate in LHO fetuses as well as between FL and 1-year survival in non-SGA patients. Prospective investigations in CHD fetuses should be carried out with internationally standardized growth charts to better examine their prognostic value in this high-risk population.

Author contributions OG: project development, data collection, data analysis and manuscript writing. FH: project development, data collection, data analysis, and manuscript writing. EO: data collection and manuscript editing. SML: data collection and manuscript editing. JUO: data collection and manuscript editing. PE: data collection and manuscript editing. AWG: data collection and manuscript editing. BH: data analysis and manuscript editing. RAF: project development and manuscript editing. CE: manuscript editing. KA: manuscript editing. AK: manuscript editing. RO: project development, data collection, data analysis and manuscript editing. BK: project development, data collection, data analysis and manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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