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Growth patterns and cerebro-placental hemodynamics in fetuses with congenital heart disease

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ABSTRACT

Objectives: Congenital heart disease (CHD) has been associated with a reduced fetal head circumference (HC). The underlying pathophysiological background remains undetermined. We aimed to define trends in fetal growth and cerebro-placental Doppler flow, and to investigate the association between head growth and cerebro-placental flow in fetuses with CHD.

Methods: Fetuses with CHD and serial measurements of HC, abdominal circumference (AC), middle cerebral artery pulsatility index (MCA-PI), umbilical artery pulsatility index (UA-PI), and cerebro-placental ratio (CPR) were included. CHD was categorized into 3 groups based on expected cerebral

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arterial oxygen saturation: normal, mild to moderately reduced, and severely reduced. Trends over time in Z-scores were analyzed using a linear mixed-effects model.

Results: 181 fetuses fulfilled the inclusion criteria. Expected cerebral arterial oxygen saturation in CHD was classified as normal in 44, mild to moderately reduced in 84 and severely reduced in 53 cases. HC z-scores showed a tendency to decrease until 23 weeks, then to increase until 33 weeks, followed by a decrease again in the late third trimester. AC increased progressively with advancing gestation. MCA-PI and UA-PI showed significant trends throughout pregnancy, but CPR did not. There were no associations between expected cerebral arterial oxygen saturation and fetal growth. Average trends in MCA-PI were significantly different in the three subgroups (P=0.010), whereas average trends in UA-PI and CPR were similar (P=0.530 and P=0.285). Furthermore, there was no significant association between MCA-PI and HC (P=0.284).

Conclusions: Fetal biometry and Doppler flow patterns are within normal ranges in fetuses with CHD, but show trends over time. Fetal head growth is not associated with the cerebral blood flow pattern or placental function and HC is not influenced by the cerebral arterial oxygen saturation.

INTRODUCTION

A number of abnormal findings have been described in fetuses with congenital heart disease (CHD). They are often small for gestational age, have smaller head circumferences (HC), and they show signs of abnormal magnetic resonance imaging such as smaller brain volumes, delayed development and white matter injuries, increasing the risk of neurodevelopmental deficiencies.[1-12] Regarding growth impairments, Rosenthal et al. proposed two underlying pathophysiological mechanisms. Either fetuses with intrinsic growth disturbances are more at risk for developmental errors during cardiogenesis, or CHD might lead to circulatory alterations (such as retrograde flow in the aortic arch), low cerebral blood flow and reduced cerebral oxygen or energy substrate delivery that are incompatible with optimal growth.[12-14]

Doppler flow patterns reflecting circulatory alterations in fetuses with CHD have been reported previously.[1,2,4-7,15-25] A lower middle cerebral artery pulsatility index (MCA-PI), a higher umbilical artery pulsatility index (UA-PI), and a lower cerebro-placental ratio (CPR) have been reported in these fetuses compared to healthy fetuses.[1,2,4-7,15-25] The exact association between circulatory alterations and fetal growth, especially HC, and by inference brain development, remains unclear however. Only a few authors have assessed the association between prenatal Doppler flow patterns and fetal growth in CHD fetuses and they were unable to demonstrate a clear association. However, these studies used a single Doppler measurement in a heterogeneous cohort of CHD.[2,5,7]

The association between fetal growth and Doppler flow patterns may be influenced by gestational age[1-2] and the nature of the cardiac defect.[1,5,6,16,19,21] Our aim was, therefore, to define trends in fetal growth and cerebro-placental Doppler flow and to investigate the relationship between fetal head growth and cerebro-placental flow in fetuses with CHD subdivided according to the expected cerebral arterial oxygen saturation.

METHODS

Study population

This was a retrospective collaborative study in two Fetal Medicine Units in The Netherlands (University Medical Center Groningen and Academic Medical Center Amsterdam). All fetuses with CHD in whom Doppler flow patterns and biometry had been measured serially after 19 weeks' gestation between January 2010 and November 2016 were included. Fetuses with chromosomal and genetic abnormalities or extracardiac malformations were excluded.

Study design

As part of routine clinical care, a fetal medicine expert measured fetal biometry and Doppler flow, including HC, abdominal circumference (AC), MCA-PI and UA-PI. Cerebro-placental ratio was calculated as MCA-PI divided by UA-PI. In addition, pulsatility index of the uterine arteries (UtA-PI) was assessed once at the first fetal echocardiogram. All available measurements of HC, AC, MCA-PI and UA-PI were retrieved starting from 19 weeks' gestation, which is the usual referral time after the routine 19-21 weeks' scan. All fetal measurements were converted into Z-scores to adjust for differences in gestational age based on previously published normative data.[26-29] In addition, a complete fetal echocardiogram was performed by a fetal medicine expert and/or an experienced pediatric cardiologist using a standardized protocol to assess fetal cardiac anatomy and function. All cardiac diagnoses, were reviewed by one pediatric cardiologist (SC). Furthermore, postnatal echocardiographic examinations and surgical reports were reviewed for fetuses who were born alive. Postmortem reports were reviewed in case of termination of pregnancy or intrauterine fetal demise. Cases with unknown pregnancy outcome were only included if fetal echocardiographic examination was sufficient to confirm the CHD diagnosis. Additional information collected from the maternal and neonatal medical files included gestational age at birth, head circumference at birth, Apgar score at 5 minutes and outcome (live born, intrauterine fetal demise, termination of pregnancy, or neonatal/infant death). Furthermore, we collected information on maternal complications (CHD, diabetes, hypertensive disorders, hypothyroidism or other) and maternal body mass index.

Congenital heart disease classification

The type of CHD was categorized by a pediatric cardiologist according to the expected cerebral arterial saturation. Much of our knowledge of the fetal circulation is derived from studies performed in fetal lambs.[30] Subsequent human fetal ultrasound studies have shown that blood flow patterns are similar in humans fetuses and lambs.[13] Currently, human fetal MRI studies, are expanding our knowledge of oxygen delivery to the brain and oxygen consumption in normal hearts and in CHD, but exact knowledge of cerebral saturations in fetal CHD is still lacking.[11,31] CHD may cause abnormal blood volume and flow patterns, altered chamber and great vessel sizes and positions, altered oxygen delivery to organs and increased venous pressure. Blood flow in the ductus venosus and arterial duct is also important. All of these factors were taken into consideration when defining three CHD categories based on the expected cerebral arterial oxygen saturation: (I) expected normal cerebral arterial oxygen saturation, (II) expected mild to moderately reduced cerebral arterial oxygen and (III) expected severely reduced cerebral arterial oxygen saturation (Table 1). Figure 1 shows the hemodynamics and saturations of several CHDs allocated to these three groups as reported by Rudolph et al.[13,14,30] Fetuses with varying degrees of left ventricular outflow tract obstruction fall into different categories depending on the intra-cardiac anatomy and degree of obstruction. In mild aortic stenosis a normal cerebral oxygen saturation is expected. In critical aortic stenosis retrograde flow over the aortic arch occurs reducing the cerebral arterial saturation, hence allocation to group II. Hypoplastic left heart syndrome (HLHS), where the entire cerebral blood flow may be dependent on retrograde flow in the aortic arch, was allocated to group III.

Sensitivity analyses

In the MRI study of Sun et al., the mean aortic saturation in human fetuses with CHD was lower than in normal hearts. Furthermore, there were differences in aortic saturation between different types of CHD. Fetuses with tetralogy of Fallot (ToF) had the highest ascending aortic saturations of the cyanotic CHDs, followed by transposition of the great arteries (TGA) (including both TGA with intact septum (+IVS) and VSD) and single ventricle lesions (predominantly HLHS and tricuspid atresia).[11] With this in mind, we repeated the analysis further subdividing the intermediate (mild to moderate)

group into 2 subgroups, with HLHS allocated to the moderate group and only TGA with intact septum (+IVS) cases to the severely reduced group (Supplemental Table 1).

As Jansen et al. reported that fetuses with ToF had smaller head circumferences, starting from 20 weeks' gestation onwards,[32] we also repeated the analyses separately for fetuses with ToF. We performed two different analyses, namely three subgroups + ToF (normal, mild to moderately reduced, severely reduced and ToF) and four subgroups + ToF (normal, mildly reduced, moderately reduced, severely reduced and ToF).

Statistical analysis

All data were entered into an IBM SPSS statistics database (version 23.0, IBM Corp., Armonk, NY, USA). Study population characteristics were described as frequencies (percentage) for categorical variables, mean (± standard deviation; SD) for continuous parameters with an approximately symmetric distribution and median (interquartile) for continuous data with a skewed distribution. Average trends over time for fetal growth (HC and AC) and Doppler flow (MCA-PI, UA-PI and CPR) were estimated using a linear mixed-effects model and analyzed with the statistical software R (version 3.4.0, Foundation for Statistical Computing, Vienna, Austria). A linear mixed-effects model takes into account repeated measurements over time and allows the number and timing of the measurements to vary per fetus. To avoid selection bias, all fetuses with at least one measurement were included in the analyses.[33] Average age trends ('fixed effects') were allowed to differ by CHD classification and were modeled by restricted cubic splines. The restricted cubic spline function allowed us to explore the effect of age without making restrictive assumptions about the shape of the time trends. Knots were placed at five fixed quintiles of the predictor's distribution as suggested by Stone.[34] Fetuses in the study population were considered to be a random sample of the total fetal CHD population. Therefore, we allowed the intercept (i.e. value at birth) and slope to differ per fetus, and assumed these parameters to follow a multivariate normal distribution ('random effects'). In addition, specific time intervals were tested based on the averaged trend. This enabled analysis of the difference in MCA-PI trends over time between fetuses with a normal HC or abnormal HC (<-2.0 or >2.0 SD) at the last measurement before birth in the total cohort and in the three different CHD categories. It also

enabled the analysis of the difference in MCA-PI trends over time between fetuses with a normal HC/AC ratio or abnormal HC/AC ratio (abnormal HC/AC ratio: $<5^{th}$ percentile or $>95^{th}$ percentile). Sampling uncertainty was quantified via 95% confidence intervals (CI) and *P*-values. A *P*-value <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

A total of 181 fetuses with CHD were included. Six fetuses (3%) died before birth, thirteen (7%) pregnancies were terminated and 22 (12%) died during the neonatal period or within the first three months after birth. Cardiac diagnosis was confirmed by fetal echocardiographic examination and postnatal echocardiographic examination or surgical reports in 86% of the cases, by fetal echocardiographic examination and postmortem reports in 4% of the cases and by fetal examination only in 10% of the cases. A total of 745 ultrasound examinations were carried out in the 181 CHD fetuses. Forty-four fetuses were allocated to the group with normal expected cerebral arterial oxygen saturation, 84 to the mild to moderately reduced group and 53 to the severely reduced group. The median number of ultrasound observations per fetus was three (interquartile 2 - 4) with a maximum of sixteen observations. Patient characteristics are presented in Table 2. Mean (±SD) UtA Z-scores were -0.44 (±1.87) for the left uterine artery and -0.75 (±2.14) for the right uterine artery. Fifteen percent of the fetuses had abnormal UtA-PI Z-scores (>2.0).

Trends in fetal biometry and Doppler flow in the entire cohort

The study included 611 HC, 632 AC, 396 MCA-PI, 465 UA-PI and 362 CPR measurements. UtA-PI was assessed in 86 fetuses (48%). All fetuses had multiple HC measurements and 60% had multiple MCA-PI measurements. There were no differences in baseline characteristics between fetuses with one and fetuses with more MCA-PI measurements. The average trends in Z-scores of fetal biometry (HC and AC) and Doppler flow (MCA-PI, UA-PI and CPR) for the entire cohort are shown in Figure 2. Average trends over time were significant in both HC (P<0.0001) and AC (P<0.0001) Z-scores. The HC Z-scores decreased from 20 weeks until 23 weeks (P=0.005), then increased thereafter until 33 weeks (P<0.0001). After 33 weeks, HC Z-scores decreased again. The AC Z-scores increased progressively during gestation. Doppler flow patterns showed a statistically significant average trend for MCA-PI (P=0.010) and UA-PI (P<0.0001), but not for CPR (P=0.161). The Z-scores of MCA-PI showed a slight increase between 25 and 30 weeks of gestational age, however this trend was not statistically significant (P=0.102) and a decrease after 30 weeks until approximately 35 weeks

(*P*=0.001). Irrespective of the observed trends, the averaged trend lines of all parameters fell within normal ranges (Z-score >-2.00 and <2.00).

Trends in fetal biometry and Doppler flow in the subgroups

In Figure 3, the average trends in Z-scores are shown per CHD group categorized according to the expected cerebral arterial oxygen saturation. There were no statistically significant differences in average trends for HC and AC among the CHD categories (*P*=0.884 and *P*=0.879 respectively). The average trends in MCA-PI were significantly different between the three subgroups (*P*=0.010), but there were no differences in the average trends for UA-PI (*P*=0.530) and CPR (*P*=0.285). Fetuses with a mild to moderately or a severely reduced expected cerebral arterial oxygen saturation showed more fluctuations in MCA-PI (*P*=0.019 and *P*<0.0001, respectively) throughout pregnancy, whereas fetuses with a normal expected cerebral arterial oxygen saturation showed no trend in MCA-PI (*P*=0.831).

MCA-PI trends according to HC before birth

Figure 4 shows the average trend in MCA-PI between fetuses with normal and abnormal HC Z-scores at the last measurement for the total cohort and for the three subgroups of CHD. Nineteen (10%) fetuses with various types of CHD had an abnormal HC Z-score at the last measurement before birth. There was no statistically significant difference in the average trend of MCA-PI between normal and abnormal HC for the total cohort (*P*=0.284) and for the subgroups of CHD (*P*=0.363). There were also no differences in the average trend of MCA-PI between normal and abnormal HC/AC ratio (*P*=0.505).

Sensitivity analyses

The average trends in Z-scores of fetal biometry and Doppler flow patterns for four different subgroups are shown in Supplemental Figure 1. The average trends for HC (*P*=0.656), AC (*P*=0.707) and CPR (*P*=0.513) did not differ between the four subgroups, whereas trends in MCA-PI and UA-PI were significantly different in the four subgroups (*P*=0.028 and *P*=0.020 respectively). When ToF was analyzed separately from the three subgroups (normal, mild to moderately reduced and severely reduced cerebral arterial oxygen saturation), similar trends in Z-scores of fetal biometry and Doppler flow patterns were observed (Supplemental Figure 2). The average trends for HC (*P*=0.950), AC (*P*=0.701) and CPR (*P*=0.152) did not differ between the subgroups. The average trends for MCA-PI (*P*=0.024) and UA-PI (*P*=<0.0001), on the other hand, were significantly different in the subgroups. When ToF cases were analyzed separately from the four subgroups (normal, mildly reduced, moderately reduced and severely reduced cerebral arterial oxygen saturation) results were also similar, with the exception that MCA-PI trends (*P*=0.073) were no longer significant (Supplemental Figure 3).

DISCUSSION

This study demonstrates that although HC, AC, MCA-PI, UA-PI and CPR remain within normal ranges, there are significant trends over time in fetuses with CHD. Trends in MCA-PI also differ between fetuses with expected normal, mild to moderately reduced or severely reduced cerebral arterial oxygen saturation, while trends in fetal growth do not differ between these subgroups. Fetuses with CHD with expected mild to moderately reduced or severely reduced cerebral arterial oxygen saturation show more fluctuations in MCA-PI throughout pregnancy. Furthermore, this study shows that there are no significant associations between MCA-PI and HC in fetuses with various types of CHD, subdivided according to the expected cerebral arterial oxygen saturation.

It has been suggested that in fetuses with CHD there is preferential blood redistribution to the brain in order to guarantee an optimal cerebral oxygen supply, as in fetal hypoxemia due to placental insufficiency. [1,2,4-7,15-25] Most of these studies used a single Doppler measurement performed during the second or third trimester.[4-7,15-25] We were unable to confirm a circulatory redistribution in favor of the brain. Doppler parameters remained within normal ranges in our cohort. However, in contrast to chronic hypoxemia, HC z-score showed a tendency to decrease at the end of the third trimester, while AC continued to increase with advancing gestation. This late head growth impairment suggests that fetuses with CHD may be unable to meet the increased metabolic demands of the developing brain at the end of pregnancy.[35] The lack of a circulatory compensation, inferred by constant MCA-PI Z-scores, in spite of the lower HC Z-scores, further supports this hypothesis.

Previous studies on serial fetal biometry and Doppler measurements in fetuses with CHD also show remarkable discrepancies. While the majority report significant trends over time in both fetal biometry and cerebro-placental Doppler flow, the directions of trends differ significantly between studies.[1,2,32] Discrepancies might be caused by differences in study methodology. For instance, we used the same statistical approach as Ruiz et al., but they assumed that the effect of gestational age followed a quadratic time trend, which may have produced the tendency for fetal parameters to increase during pregnancy.[1] We made no assumptions regarding the shape of the time trend as we do not know whether use of a quadratic trend is justified. Furthermore, the discrepancies might be caused

by differences in study population, although the populations are fairly representative of the most commonly found CHD during fetal life.[1,32]

Since fetal brain development is dependent on adequate oxygen and nutrient supply, it has been hypothesized that fetuses with CHD in whom umbilical venous blood, rich in nutrients and oxygen, is partly shunted away from the brain have impaired cerebral development.[1,5,6,19,22] Several studies reported lower MCA-PI and CPR and higher UA-PI in CHD with low expected cerebral oxygen supply.[1,5,6,19,22] We were unable to confirm this circulatory redistribution, but we did observe more fluctuations in MCA-PI throughout pregnancy. These fluctuations may be an important observation. Although we cannot exclude that they are physiological variations as longitudinal studies in healthy fetuses are lacking, we speculate that, if real, the fluctuations might be harmful for the development of the brain. They might suggest an impaired hemodynamic autoregulation, that, analogous to what is known in preterm infants,[36,37] may have a harmful effect on the vulnerable developing brain.

There were, however, no associations between MCA-PI and HC in the entire cohort nor in the three CHD subgroups. Previous studies were also unable to demonstrate a clear association between MCA-PI and HC. Furthermore, Jansen et al. found no association between the flow in the ascending aorta and HC.[32] These studies, however, were either based on univariate statistical analyses or only used theoretical hemodynamics. We used multivariate statistical analyses and measured MCA-PI. Therefore, we believe that our study is more robust and we speculate that head growth might be more dependent on other factors such as maternal, (epi)genetic factors, or nutrients (glucose)[31] than on blood flow to the brain.

This study has several strengths and limitations. It is the first study that assesses the association between trends in Doppler flow and fetal growth in a relatively large cohort of consecutively seen fetuses with CHD. Furthermore, we included an unselected population (the assessment of fetal growth and cerebro-placental Doppler flow was part of routine clinical care in both institutions) and we excluded all cases with chromosomal abnormalities, including microdeletions. However, this was a retrospective study, operators were not blinded to the presence of CHD, which might have affected Doppler and biometry measurements, and the assessment of Doppler

flow was not standardized, resulting in various numbers of measurements across the whole range of gestational ages of the fetuses. Nonetheless, there were no indications that missing data in the cohort are not at random. Therefore, our linear-mixed effects model provides an unbiased estimate of the age trends. In addition, we were unable to confirm cardiac diagnosis using postnatal echocardiograms, surgery reports or postmortem reports in 10% of the cases. Furthermore, differences in study populations, reference charts used and study design, limit comparisons with other studies. We believe that our classification of fetuses into normal, mild to moderately reduced, and severely reduced expected cerebral arterial oxygen saturation is based on the best data currently available,[11,13,14,30,31] however this remains speculative as it is impossible to directly measure oxygen levels prenatally. We thus also performed a sensitivity analysis with a slightly different classification and the results remained unchanged. Finally, we were unable to analyze each type of CHD separately due to the relatively small numbers, with the exception of ToF, notoriously associated with smaller HC[32], and TGA+IVS, where the lowest cerebral arterial oxygen saturation is expected. Larger multicenter studies, allowing for larger groups with the same type of CHD, are necessary to provide insights into possible mechanisms responsible for suboptimal intra-uterine cerebral development in a specific heart lesion.

In conclusion, this study demonstrates that while there are significant trends in biometry and Doppler flow throughout pregnancy in fetuses with CHD, these measurements are within normal ranges. Fetal head growth is not associated with the expected cerebral arterial oxygen saturation or fetal Doppler flow, confirming that other mechanisms than circulatory modifications may influence the cerebral development in fetuses with CHD.

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FIGURE LEGENDS

Figure 1 Classification of fetal congenital heart defects according to expected cerebral arterial oxygen saturation with three examples from each category (adapted from Rudolph),[13,14,30] I normal: A. normal heart; B. coarctation of the aorta; C. mild to moderate aortic stenosis; II mild to moderately reduced: A. tetralogy of Fallot, B. pulmonary atresia with intact septum, C. critical aortic stenosis; and III severely reduced: A. TGA with VSD; B. TGA with intact interventricular septum; C. hypoplastic left heart syndrome (aortic and mitral atresia). Saturations are based on lamb experiments and may be lower in the human fetus. Flow hemodynamics are illustrated by arrows. Ao, descending aorta; DA, arterial duct; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; TGA, transposition of the great arteries; VCI, inferior vena cava VCS, superior vena cava; VSD, ventricular septal defect.

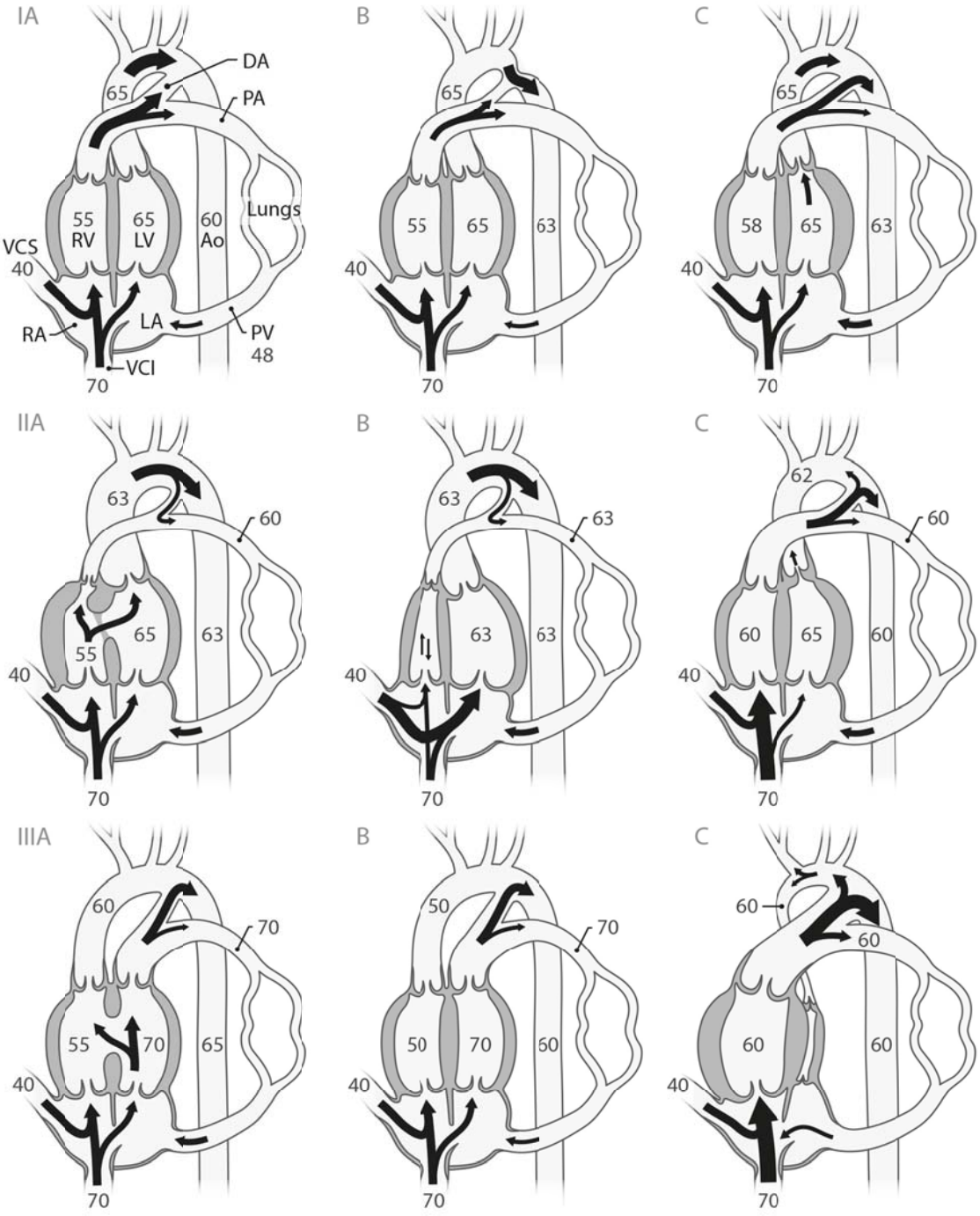


Figure 2 Averaged trends in Z-score of fetal growth (dark blue) and Doppler flow patterns (light blue). A. HC, head circumference; B. AC, abdominal circumference; C. MCA-PI, middle cerebral artery pulsatility index; D. UA-PI, umbilical artery pulsatility index; E. CPR, cerebro-placental ratio. Gray dots are individual measurements, and grey lines are individual trends. The 95% confidence intervals for the fitted model are shown in dark grey.

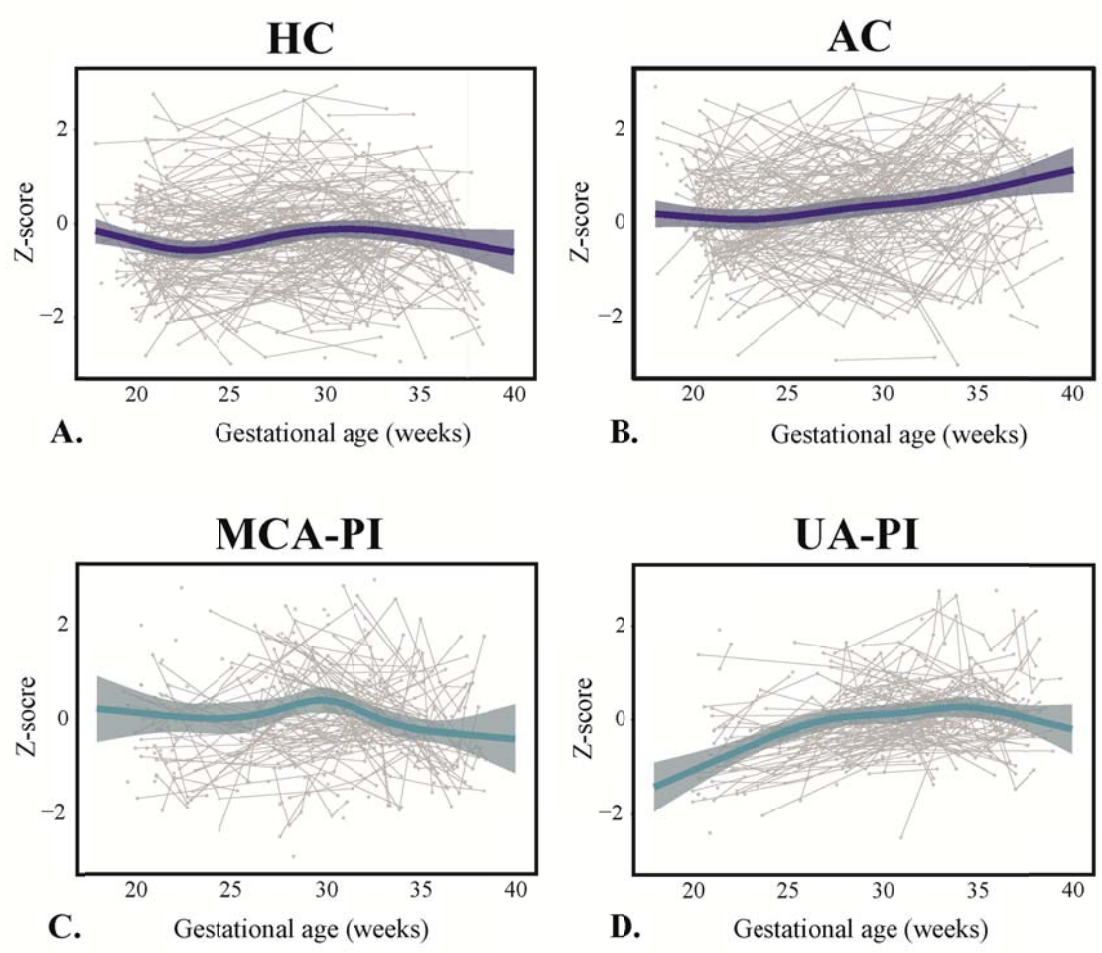


Figure 3 Averaged trends in Z-score of fetal growth and Doppler flow by CHD category.

A. HC, head circumference; B. AC, abdominal circumference; C. MCA-PI, middle cerebral artery pulsatility index; D. UA-PI, umbilical artery pulsatility index; E. CPR, cerebro-placental ratio. Normal, normal expected cerebral arterial oxygen saturation; Mild to moderately reduced, mild to moderately expected cerebral arterial oxygen saturation; Severely reduced, severely reduced expected cerebral arterial oxygen saturation. The 95% confidence intervals of the fitted model are shown in grey.

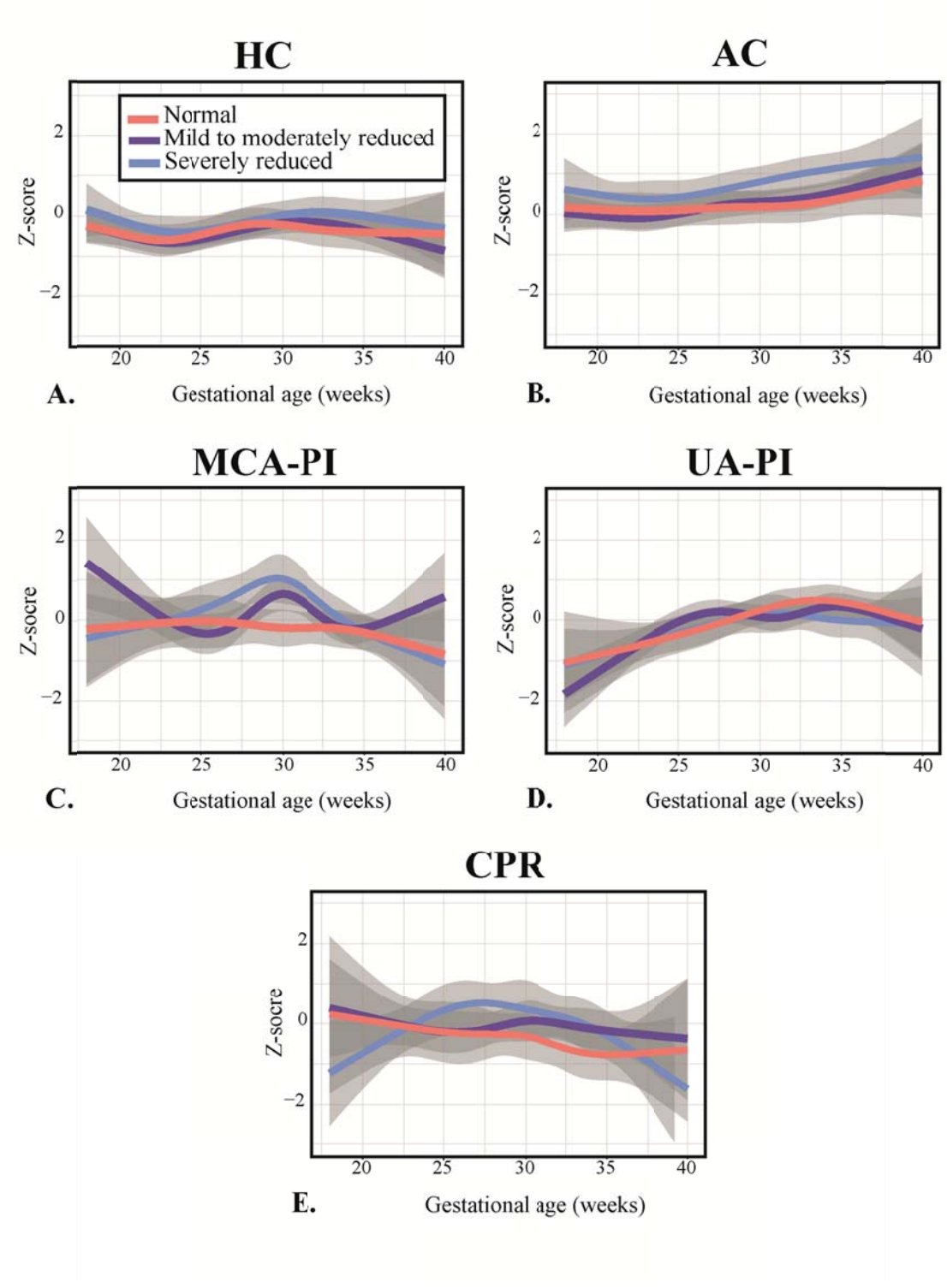
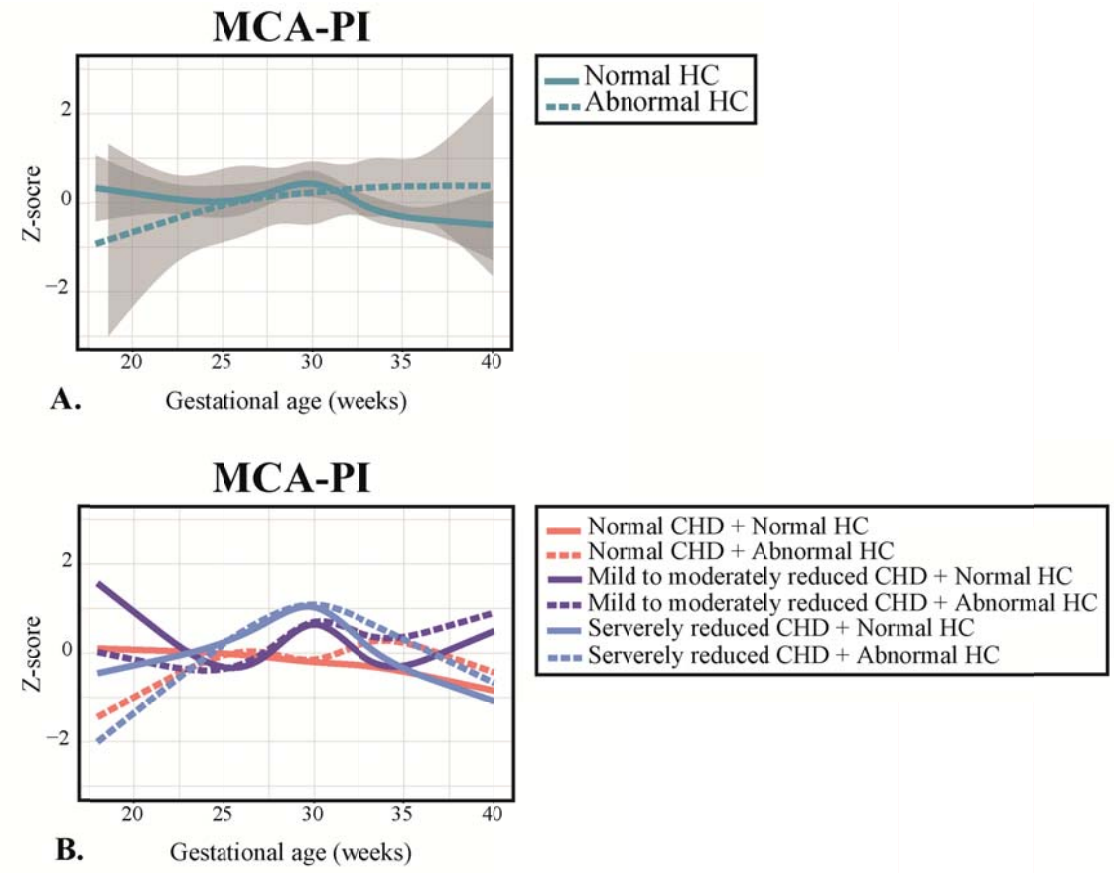


Figure 4 Average trends in Z-score of MCA-PI for normal and abnormal HC in (A) the total cohort and (B) for CHD categories. MCA-PI, middle cerebral artery pulsatility index; HC, head circumference; Normal CHD, normal expected cerebral arterial oxygen saturation; Mild to moderately reduced CHD, mild to moderately reduced expected cerebral arterial oxygen saturation; Severely reduced CHD, severely reduced expected cerebral arterial oxygen saturation. The 95% confidence intervals of the fitted model are only shown for the total cohort in grey. In the average trends for the CHD categories the 95% confidence intervals are broad and overlapping.



Supplemental Figure 1 Averaged trends in Z-score of fetal growth and Doppler flow by CHD category. A. HC, head circumference; B. AC, abdominal circumference; C. MCA-PI, middle cerebral artery pulsatility index; D. UA-PI, umbilical artery pulsatility index; E. CPR, cerebro-placental ratio. Normal, normal expected cerebral arterial oxygen saturation; Mildly reduced, mildly reduced expected cerebral arterial oxygen saturation; moderately reduced, moderately reduced expected cerebral arterial oxygen saturation; Severely reduced, severely reduced expected cerebral arterial oxygen saturation. The 95% confidence intervals of the fitted model are shown in grey.

Supplemental Figure 2 Averaged trends in Z-score of fetal growth and Doppler flow by CHD category. A. HC, head circumference; B. AC, abdominal circumference; C. MCA-PI, middle cerebral artery pulsatility index; D. UA-PI, umbilical artery pulsatility index; E. CPR, cerebro-placental ratio. The 95% confidence intervals of the fitted model are shown in grey. Normal, normal expected cerebral arterial oxygen saturation; Mild to moderately reduced, mild to moderately expected cerebral arterial oxygen saturation; Severely reduced, severely reduced expected cerebral arterial oxygen saturation; ToF, tetralogy of Fallot. The 95% confidence intervals of the fitted model are shown in grey.

Supplemental Figure 3 Averaged trends in Z-score of fetal growth and Doppler flow by CHD category. A. HC, head circumference; B. AC, abdominal circumference; C. MCA-PI, middle cerebral artery pulsatility index; D. UA-PI, umbilical artery pulsatility index; E. CPR, cerebro-placental ratio. The 95% confidence intervals of the fitted model are shown in grey. Normal, normal expected cerebral arterial oxygen saturation; Mildly reduced, mildly reduced expected cerebral arterial oxygen saturation; Moderately reduced, moderately reduced expected cerebral arterial oxygen saturation; Severely reduced, severely reduced expected cerebral arterial oxygen saturation; ToF, tetralogy of Fallot. The 95% confidence intervals of the fitted model are shown in grey.

TABLES

Table 1 Congenital heart disease classification according to the expected cerebral arterial oxygen saturation

Expected normal cerebral arterial saturation	**N = 44**
Atrio-ventricular septal defect (AVSD), (1 with left isomerism, 1 with atrial septal defect (ASD))	10
Isolated ventricular septal defect (VSD)/VSDs	13
VSD + ASD (1 with absent ductus venosus)	2
Moderate aortic stenosis (AS), (1 with pulmonary stenosis (PS))	2
Coarctation of the aorta (CoA)	6
PS and dysplastic pulmonary valve	5
Tricuspid valve abnormalities (antegrade flow over the aortic arch)	2
Double discordance with Ebstein's anomaly (antegrade flow over the aortic arch)	1
Mitral stenosis (MS) including small left ventricle (LV) (antegrade flow over the aortic arch)	3
Mild to moderately reduced cerebral arterial saturation	**N = 84**
AS (critical, retrograde flow over the aortic arch)	1
CoA with VSD (+/- AS or hypoplastic aortic arch)	10
Interrupted aortic arch with VSD	2
Ebstein's anomaly (retrograde flow in arterial duct (+/- PS/ pulmonary atresia (PA), 1 with small VSD)	5
PS with VSD (1)/Tetralogy of Fallot (14)/Double outlet right ventricle (DORV) with PS (4)	19
PA with VSD	4
DORV with atrioventricular discordance and CoA	1
DORV with mal/transposition of the great arteries with PS	4
DORV with mal/transposition of the great arteries (+/- CoA or hypoplastic LV, no PS or Taussig-Bing)	4
Transposition of the great arteries (TGA) with PS and MS	1
Common arterial trunk (1 with AVSD)	7
PA with intact ventricular septum (IVS)	5
Tricuspid atresia (TA) (+/- mal/transposition of the great arteries, hypoplastic aortic arch, PS or DORV, 1 with infracardiac TAPVD)	7
Hypoplastic right heart (TA/tricuspid stenosis with PA and IVS or critical PS with hypoplastic right ventricle (RV))	6
Double inlet left ventricle (+/- TGA with hypoplastic aortic arch PA, 1 with AVSD and right isomerism)	7
Complex: Criss-cross heart, AVSD, PA, aorta out RV, PAPVD, right isomerism	1
Severely reduced cerebral arterial saturation	**N = 53**
Hypoplastic left heart syndrome (aortic atresia +/- mitral atresia/ stenosis), (2 with AVSD)	16
TGA with VSD	10
DORV with TGA (Taussig-Bing) +/- hypoplastic aortic arch	3
TGA with IVS	24

AVSD, atrio-ventricular septal defect; ASD, atrial septal defect; VSD, ventricular septal defect; AS, aortic stenosis; PS, pulmonary stenosis; CoA, coarctation of the aorta; MS, mitral stenosis; LV, left ventricle; PA, pulmonary atresia; DORV, double outlet right ventricle; TGA, transposition of the great arteries; TA, tricuspid atresia; IVS, intact ventricular septum; TAPVD, total anomalous pulmonary venous drainage; RV, right ventricle; PAPVD, partial anomalous pulmonary venous drainage

Table 2 Patient characteristics

	N=181
Maternal BMI (kg/m^2)	24.8 (4.6)
Maternal Smoking	17 (9)
Maternal illness	
No maternal illness	151 (83)
CHD	2 (1)
Diabetes	6 (3)
Hypothyroidism	1 (1)
Other*	9 (5)
Nulliparous	61 (34)
UtA-PI	-0.44 (1.87)
Outcome	
Live born	122 (68)
IUFD	6 (3)
TOP	13 (7)
NND/ID	22 (12)
Unknown	17 (10)
Gestational age at birth (weeks)	37.5 (4.32)
Birth weight (grams)	3055 (802)
Head circumference at birth (cm)	33.4 (3.16)
Apgar score 5 minutes	9 (1.27)

*Data are presented as either mean (SD) or number (percentage). CHD, congenital heart disease; IUFD, intrauterine fetal demise; TOP, termination of pregnancy; NND/ID, neonatal or infant death. *hyperthyroidism, pituitary gland pathology, congenital hepatic fibrosis, or migraine.*