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**RESEARCH**

# Effects of congenital heart disease on fetal growth and neurodevelopment: evaluation of fetuses in the second and third trimesters of gestation

## Konjenital kalp hastalığının fetal büyüme ve nörogelişim üzerindeki etkileri: Gebeliğin ikinci ve üçüncü trimesterlerinde fetüslerin değerlendirilmesi

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**Abstract**

**Purpose:** The aim of this study is to evaluate the neurodevelopmental prognosis of fetuses with congenital heart defects by considering aortic flow and oxygen saturation in the ascending aorta, and to investigate them in terms of cortical developmental delay.

**Materials and Methods:** In this retrospective study, neurosonographic and hemodynamic parameters were measured in fetuses diagnosed with congenital heart defects. These measurements were compared with those of gestational-age-matched low-risk controls in the second and third trimesters. Standard fetal biometry, transcerebellar diameter, Sylvian fissure area, and related ratios were evaluated.

**Results:** The study included 53 fetuses with congenital heart defects and 72 controls in the second trimester, and 72 fetuses with congenital heart defects and 58 controls in the third trimester. In the second trimester, the Sylvian fissure area was lower in the CHD group (50.98 ± 21.02 $mm^2$ vs 58.37 ± 16.41 $mm^2$), while the HC/SYL ratio was higher in the CHD group in both the second trimester (4.53 ± 1.69 vs 3.44 ± 0.74) and the third trimester (2.71 ± 1.31 vs 2.09 ± 0.49). Neurodevelopmental parameters showed that the Sylvian fissure area was smaller in the second-trimester congenital heart defects group compared with controls. Consequently, the aortic valve diameter/Sylvian fissure area and head circumference/Sylvian fissure area ratios were higher in the congenital heart defects group. In the third trimester, patients with normal aortic flow and two functional ventricles had higher aortic valve diameter/Sylvian fissure area ratios than other patient groups.

**Conclusion:** Detecting early-onset cortical developmental delay in patients with left cardiac dysfunction using proportional data is crucial for a holistic approach to

**Öz**

**Amaç:** Bu çalışmanın amacı, aortik akım ve çıkan aortadaki oksijen satürasyonu göz önünde bulundurularak doğumsal kalp anomalili fetusların nörogelişimsel prognozunun değerlendirilmesi ve kortikal gelişim geriliği açısından incelenmesidir.

**Gereç ve Yöntem:** Bu çalışmada, doğumsal kalp anomali tanısı alan fetuslarda nörosonografik ve hemodinamik parametreler ölçüldü. Bu ölçümler, ikinci ve üçüncü trimesterde gebelik haftasına göre eşleştirilmiş düşük riskli kontrol grubu ile karşılaştırıldı. Standart fetal biyometri ölçümlerine ek olarak transserebellar çap, Sylvian fissür alanı ve ilişkili oranlar değerlendirildi.

**Bulgular:** Çalışmaya, ikinci trimester döneminde yer alan 53 doğumsal kalp anomali tanılı fetus ile 72 sağlıklı kontrol olgusu ve üçüncü üçay dönemindeki 72 doğumsal kalp anomali tanılı fetus ile 58 kontrol olgusu dâhil edilmiştir. 2. trimesterde SYL alanı CHD grubunda daha düşük: 50,98 ± 21,02 $mm^2$ vs 58,37 ± 16,41 $mm^2$, HC/SYL oranı CHD grubunda daha yüksek: 2. trimesterde 4,53 ± 1,69 vs 3,44 ± 0,74, 3. trimesterde 2,71 ± 1,31 vs 2,09 ± 0,49. Nörolojik gelişimi yansıtan ölçütler değerlendirildiğinde, ikinci trimester grubunda yer alan doğumsal kalp anomalili fetuslarda kontrol grubuna göre Sylvius oluğu alanının daha küçük olduğu, buna bağlı olarak kafa çevresi/Sylvius alanı ve aort/Sylvius alanı oranlarının belirgin şekilde yüksek bulunduğu saptanmıştır. Üçüncü trimester normal aort akımı bulunan ve iki ventrikülü fonksiyonel olan fetuslarda, diğer gruplara göre aort/Sylvius alanı oranı daha yüksek saptanmıştır.

**Sonuç:** Sol kardiyak disfonksiyonlu hastalarda erken dönemde başlayan kortikal gelişim geriliğinin oransal veriler üzerinden tespit edilmesi değerlendirmeye bütüncül yaklaşım açısından önem arz etmektedir. Baş çevresi/Sylvian fissür alanı ve aort kapak çapı/Sylvian

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evaluation. Incorporating head circumference/Sylvian fissure area and aortic valve diameter/Sylvian fissure area ratios into routine prenatal follow-up measurements may help identify fetuses at potential risk for adverse postnatal neurodevelopmental outcomes.
**Keywords:** Heart defects, congenital, neurodevelopmental disorders, sylvian fissure, prenatal diagnosis

fissür alanı oranlarının rutin doğum öncesi takip ölçümlerine dahil edilmesi, doğum sonrası olumsuz nörogelişimsel sonuçlar açısından potansiyel risk altında olan fetüslerin belirlenmesine yardımcı olabilir.

**Anahtar kelimeler**: Kardiyak defektler, konjenital, nörogelişimsel gerilik, sylvius oluğu, prenatal tanı

## INTRODUCTION

The prevalence of congenital heart defects (CHDs) is estimated to be around 0.5–1%. They are responsible for 7% of deaths in the neonatal period and 3% of deaths in the first year of life [1, 2]. Nearly one-quarter of newborns with congenital heart disease need a surgical procedure during their first year of life[3].

Over the last few decades, advancements in ultrasonography and specialist training, together with improvements in surgical management of CHDs, have enabled the survival of many infants who previously had a dismal prognosis. As survival has improved, new challenges have come to the forefront—most notably, suboptimal somatic growth and neurodevelopmental delay in children with CHDs[4].

Initially, debate centered on whether these problems were related to the intrauterine period, postnatal circulatory characteristics, or as consequences of cardiac surgery and related treatments. Over time, it has been shown that all of these factors influence outcome[5]. Intrauterine contributors have been demonstrated on prenatal sonographic assessments. Notably, even term infants with CHDs can exhibit white-matter underdevelopment similar to that seen in preterm infants[6]. While there are studies suggesting that white matter developmental deficiency stems from the intrauterine period, limited data are available on cortical development. The earliest sign of cortical maturation is the appearance of the Sylvian fissure, a key landmark delineating the frontal, parietal, and temporal lobes and anchoring the anatomical localization of the frontal cortex[7]. It becomes noticeable from mid-pregnancy and continues to develop through the third trimester. The Sylvian fissure is a sensitive indicator of typical cortical development[8-10]. Prior studies have characterized its normal development using shape features and quantitative measurements[11, 12, 13].

The objective of this research was to evaluate biometric parameters acquired from pregnancies with CHDs diagnosed at the Department of Obstetrics and Gynecology, Department of Perinatology, Çukurova University Faculty of Medicine, with those of a control group of the same gestational age, and to evaluate their relationship with the existing literature. While prior work includes ultrasonographic and fetal magnetic resonance imaging studies of cortical developmental delay in CHDs, these reports are limited by small patient numbers; consequently, heterogeneity exists across studies. This study offers a comprehensive assessment for early detection of cortical developmental delay in fetuses with CHDs and for examining its relationship with fetal growth parameters and aortic flow.

We hypothesized that hemodynamic compromise in fetuses with CHD leads to delays in cortical maturation, which can be quantified using Sylvian fissure morphometry and its ratio to head size and aortic diameter.

## MATERIALS AND METHODS

This retrospective observational study was conducted at the Perinatology Unit of the Department of Obstetrics and Gynecology, Çukurova University Faculty of Medicine, between October 24, 2014, and May 1, 2019. This study was approved by the Çukurova University Faculty of Medicine Ethics Committee for Non-Interventional Clinical Studies (approval no. 94, decision date: December 6, 2019). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of the study, informed consent was waived by the ethics committee. Written informed consent was obtained from all participants included in the study.

### Sample

The study population consisted of pregnant women with a prenatal diagnosis of a major structural fetal cardiac anomaly. The inclusion criterion was the presence of a prenatally diagnosed major congenital

heart defect. Exclusion criteria were a gestational age of less than 17 weeks at evaluation; the presence of any major non-cardiac structural anomaly suggestive of chromosomal defects; concomitant fetal arrhythmia; maternal conditions potentially affecting fetal growth or neurodevelopment (including pregestational diabetes mellitus, thyroid disease, preeclampsia or chronic hypertension); multiple pregnancy; fetal anemia; extensive placental bleeding or infarction suggestive of uteroplacental insufficiency and abnormal uterine artery Doppler findings. Since this study was conducted as a retrospective study, comprehensive genetic testing was not available for every case. Due to the retrospective nature of the records, consistent data on maternal body mass index, smoking status, and parity were not available for all control subjects.

The control group consisted of low-risk, gestational age–matched pregnancies evaluated consecutively after each index case during the same clinic session. Fetuses in the control group demonstrated normal biometric measurements and normal anatomical findings on ultrasonographic examination and did not meet any of the exclusion criteria applied to the study group.

## Ultrasound examination and measurements

All ultrasonographic measurements were performed by experienced perinatologists. While formal inter-observer variability analysis was not conducted retrospectively, standard imaging planes were strictly adhered to according to ISUOG guidelines. All scans were conducted using GE Voluson 730 Pro and GE Voluson E6 ultrasound systems (GE Healthcare, Zipf, Austria) equipped with an RAB 4–8 MHz volumetric convex transducer. All examinations were carried out in accordance with the guidelines of the International Society of Obstetric and Gynecologic Ultrasound (ISUOG) for mid-trimester fetal anomaly screening and fetal cardiac assessment[14].

All ultrasound images were digitally archived in the ViewPoint® 6.0 hospital imaging system, and study data were retrieved retrospectively from these stored records.Standard fetal biometric measurements included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and estimated fetal weight (EFW). In addition to routine biometry, the following neurosonographic and hemodynamic parameters were assessed: transcerebellar diameter (TCD), Sylvian fissure area (SYL), the ratio of head circumference to Sylvian fissure area (HC/SYL), and the ratio of aortic valve diameter to Sylvian fissure area (AO/SYL). Participants were assigned to gestational age–based subgroups according to the timing of the ultrasound examination. Fetuses examined between 17+0 and 26+6 weeks of gestation were classified as the second-trimester group, whereas those examined at ≥27+0 weeks were classified as the third-trimester group.

Outcome measures included comparisons of biometric and neurosonographic parameters between fetuses with congenital heart defects and gestational age–matched control fetuses within each trimester. Secondary analyses compared subgroups according to ascending aortic oxygenation status, the presence or absence of antegrade aortic flow, and combined classification systems incorporating these hemodynamic parameters.

## Classification of congenital heart defects

Patients underwent follow-up ultrasonographic examinations at approximately 6-week intervals. For analytical purposes, CHDs were classified using two literature-based classification systems in order to evaluate the relationship between cardiac hemodynamics and neurodevelopmental parameters.

## Classification according to ascending aortic oxygenation and aortic arch flow

Based on the classification proposed by Jansen et al.[15], CHDs were categorized according to (i) oxygen saturation in the ascending aorta and (ii) flow pattern within the aortic arch. Combined categories derived from these two parameters were used for subgroup analyses.

1. Ascending aortic oxygenation
    a. Low cerebral oxygenation: transposition of the great arteries (TGA)
    b. Intracardiac mixing: atrioventricular septal defect (AVSD)
    c. Normal oxygenation: congenitally corrected transposition of the great arteries and Ebstein anomaly
2. Aortic arch flow pattern
    a. Reversed aortic arch flow: aortic atresia, hypoplastic left heart syndrome

b. Obstructed aortic arch flow: aortic stenosis, aortic hypoplasia

c. Normal aortic arch flow: tetralogy of Fallot, transposition of the great arteries

## Classification based on ventricular physiology and aortic arch obstruction

To enable sensitivity analyses, a second classification system adapted from Clancy et al. was applied[14]. In this framework, fetuses with CHDs were stratified according to ventricular physiology combined with the presence or absence of aortic arch obstruction:

Class 1: Biventricular physiology without aortic arch obstruction

Class 2: Biventricular physiology with aortic arch obstruction

Class 3: Single-ventricle physiology without aortic arch obstruction

Class 4: Single-ventricle physiology with aortic arch obstruction

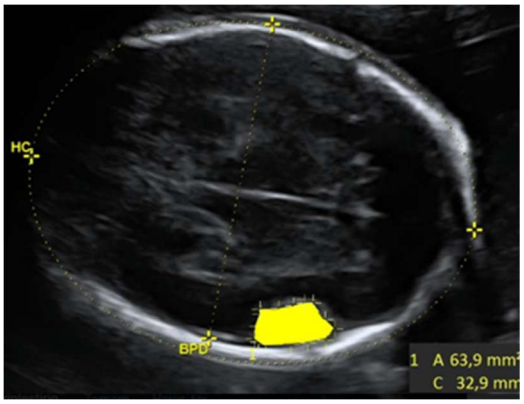


**Figure 1. Measurement of the Sylvian fissure area on the standardizaed imaging plane.**

## Assessment of cortical development

The Sylvian fissure represents one of the most dynamic structures of the developing cerebral cortex and serves as a key anatomical marker of gyral formation[17]. Its development reflects the process of opercularization, which involves progressive overgrowth of the surrounding frontal, parietal, and temporal lobes over the insula. The prenatal and postnatal morphological evolution of the Sylvian fissure follows a characteristic pattern that has been well described in the literature.

For quantitative assessment, perpendicular linear measurements were obtained from the insular cortex to the inner table of the parietal bone, representing fissure depth[10,18]. In addition, the Sylvian fissure area was quantified by planimetric tracing along the visible fissure margins on a standardized imaging plane, as illustrated in Figure 1.

## Hemodynamic measurements

Among cardiac hemodynamic parameters, the diameters of the aortic and pulmonary valves were measured, and the velocity–time integrals (VTI) of both valves were calculated. These measurements were used to evaluate fetal hemodynamic status and to derive ratios integrating cardiac output–related parameters with neurodevelopmental indices.

## Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY). Continuous variables were assessed for normality using visual (histograms and Q–Q plots) and analytical methods. Normally distributed continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test, whereas non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test.

Gestational age and quantitative fetal, neurosonographic, and hemodynamic measurements (including BPD, HC, AC, FL, EFW, TCD, SYL area, HC/SYL, and AO/SYL) were treated as continuous variables and were compared using parametric or nonparametric tests according to their distribution. Categorical variables, including subgroup classifications, were presented as frequencies and percentages and were compared using Pearson's $\chi^2$ test or Fisher's exact test, as appropriate. Relative risk (RR) estimates with corresponding 95% confidence intervals (CIs) were calculated to assess the association between congenital heart disease status and selected outcome measures. All statistical tests were two-tailed, and a p-value $< 0.05$ was considered statistically significant.

# RESULTS

Pregnancies with fetuses diagnosed with congenital heart defects CHDs in the second and third trimesters, and meeting eligibility criteria, were

compared with gestational-age–matched controls on gestational age (GA) at assessment, standard fetal biometry (BPD, HC, AC, FL, EFW), HC/EFW, HC/SYL, TCD, SYL area, and AO/SYL. CHD cases were further stratified by ascending aortic oxygenation category, aortic arch forward-flow pattern, ventricular physiology, and aortic obstruction status, and these subgroups were compared accordingly.

In the second-trimester patient group, 53 CHD cases and 72 controls were included. GA at diagnosis scan was 22.15 ± 1.73 weeks in the CHDs group and 21.50 ± 1.18 weeks in controls; no significant difference was observed ($p = 0.13$).

In the third trimester, the number of pregnant women diagnosed with CHDs was 72, while the control group consisted of 58 pregnant women with CHDs. The mean gestational age of pregnancies with CHDs was 31.61 ± 2.64 weeks, compared to 31.05 ± 2.82 weeks in the control group. No significant difference was observed between the study and control groups in the third-trimester patient group ($p = 0.25$).

When the second-trimester patient groups were compared, no significant differences were found between the fetuses diagnosed with CHDs and the control fetuses in terms of BPD, HC, AC, FL, EFW, HC/EFW or TCD measurements. Fetal biometric measurements (BPD, HC, AC, FL, EFW), SYL, TCD, and the HC/TCD, HC/SYL, and AO/SYL ratios obtained from examinations of the study and control groups in the second and third trimesters are compared in Tables 1 and 2, indicating the number of patients for whom measurements were available. Because the database was reviewed retrospectively, some patients in the study group did not have data available for each parameter.

The mean Sylvian fissure area measurement was 50.98 ± 21.02 $mm^2$ in 44 fetuses diagnosed with CHDs and 58.37 ± 16.41 $mm^2$ in 72 fetuses in the control group. In the second-trimester cohort, Sylvian fissure surface area measurements were smaller in fetuses with CHDs compared with the control group, and this difference was found to be statistically significant ($p = 0.04$).

In examinations performed at six-week intervals, fetuses with CHDs showed smaller Sylvian fissure depth measurements compared with the control group as gestational age advanced. Specifically, the depth of the Sylvian fissure was smaller in the patient group with left heart outflow obstruction than in those with right heart outflow obstruction or TGA. These findings suggest that the presence of CHDs is related to reduced cerebral fissure depth measurements in the intrauterine period.

Considering the differences in the mean HC/EFW ratio, fetuses diagnosed with CHDs had smaller head circumferences compared to normal fetuses. This smaller HC was particularly evident in fetuses with hypoplastic left heart syndrome (HLHS).

Table 1 also compares the ratios of HC measurement and aortic valve measurement to the Sylvian fissure area between the patient groups. When comparing the HC/SYL ratio of 44 fetuses diagnosed with CHDs to the 72 control groups, the study group value was 4.53 ± 1.69, while the control group value was 3.44 ± 0.74. The HC/SYL ratio in the study group was significantly higher than in the control group ($p<0.001$).

Thirty-five fetuses in the study group were compared with 72 fetuses in the control group in terms of the AO/SYL ratio. The AO/SYL ratio in fetuses diagnosed with CHDs was 0.09±0.04, and in the control group was 0.06±0.01. The AO/SYL ratio in the study group was significantly greater than in the control group ($p<0.001$).

Table 2 compares the measurements taken in fetuses with CHDs in the third trimester of pregnancy and those in the control group. Since the database was reviewed retrospectively, some patients in the study group did not have data available for every parameter.

Among the measurements performed, there were no significant differences between the two groups in terms of BPD, HC, AC, FL, EFW, TCD, SYL, or HC/EFW. However, unlike the study group with a second-trimester gestational age, no difference was observed in Sylvian fissure area measurements between the study and control groups in the third-trimester patient group. The mean Sylvian fissure area was 129 ± 55.1 $mm^2$ in 49 fetuses with CHDs and 146.72 ± 39.58 $mm^2$ in 58 patients in the control group. Although the mean Sylvius area measurement appeared larger in the control group fetuses, the difference was not statistically significant ($p = 0.06$).

**Table 1. Comparison of measurements between fetuses diagnosed with CHDs and control group fetuses in the second trimester**

| Parameter | Groups | N | Mean value | Standard deviation | Standard Error of Mean | p |
|---|---|---|---|---|---|---|
| BPD | Study group | 53 | 52.96 | 5.58 | 0.77 | 0.05 |
| | Control group | 72 | 51.29 | 4.05 | 0.48 | |
| HC | Study group | 53 | 190.50 | 21.29 | 2.92 | 0.11 |
| | Control group | 72 | 189.79 | 13.58 | 1.60 | |
| AC | Study group | 53 | 174.85 | 21.12 | 2.90 | 0.87 |
| | Control group | 72 | 171.19 | 14.24 | 1.68 | |
| FL | Study group | 53 | 38.34 | 5.08 | 0.70 | 0.07 |
| | Control group | 72 | 37.34 | 3.46 | 0.41 | |
| EFW | Study group | 53 | 507.87 | 144.52 | 19.85 | 0.13 |
| | Control group | 72 | 498.01 | 95.31 | 11.23 | |
| HC/EFW | Study group | 53 | 0.41 | 0.09 | 0.01 | 0.06 |
| | Control group | 72 | 0.44 | 0.06 | 0.01 | |
| HC/SYL | Study group | 44 | 4.53 | 1.69 | 0.26 | <0.001 |
| | Control group | 72 | 3.44 | 0.74 | 0.09 | |
| TCD | Study group | 49 | 23.48 | 2.78 | 0.40 | 0.06 |
| | Control group | 72 | 23.62 | 1.87 | 0.22 | |
| SYL | Study group | 44 | 50.98 | 21.02 | 3.17 | 0.04 |
| | Control group | 72 | 58.37 | 16.41 | 1.93 | |
| AO/SYL | Study group | 35 | 0.09 | 0.04 | 0.01 | <0.001 |
| | Control group | 72 | 0.06 | 0.01 | <0.001 | |

BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight, SYL: Sylvian fissure area, TCD: Transcerebellar diameter, AO: Aortic valve diameter

**Table 2. Comparison of measurements of third-trimester CHD-diagnosed fetuses and control group fetuses**

| Parameter | Groups | N | Mean value | Standard deviation | Standard Error of Mean | P |
|---|---|---|---|---|---|---|
| BPD | Study group | 72 | 78.89 | 6.93 | 0.82 | 0.49 |
| | Control group | 58 | 78.02 | 7.21 | 0.95 | |
| HC | Study group | 72 | 291.21 | 21.14 | 2.49 | 0.63 |
| | Control group | 58 | 289.25 | 25.10 | 3.30 | |
| AC | Study group | 72 | 275.68 | 34.95 | 4.12 | 0.31 |
| | Control group | 58 | 269.76 | 30.75 | 4.04 | |
| FL | Study group | 72 | 59.97 | 6.00 | 0.71 | 0.64 |
| | Control group | 58 | 59.42 | 7.35 | 0.97 | |
| EFW | Study group | 72 | 1865.63 | 591.46 | 69.70 | 0.47 |
| | Control group | 58 | 1790.03 | 584.69 | 76.77 | |
| HC/EFW | Study group | 72 | 0.17 | 0.04 | 0.01 | 0.47 |
| | Control group | 58 | 0.17 | 0.04 | 0.01 | |
| HC/SYL | Study group | 49 | 2.71 | 1.31 | 0.19 | <0.001 |
| | Control group | 58 | 2.09 | 0.49 | 0.06 | |
| TCD | Study group | 51 | 38.97 | 5.16 | 0.72 | 1.00 |
| | Control group | 58 | 38.97 | 5.72 | 0.75 | |
| SYL | Study group | 49 | 129.00 | 55.10 | 7.87 | 0.06 |
| | Control group | 58 | 146.72 | 39.58 | 5.20 | |
| AO/SYL | Study group | 36 | 0.06 | 0.04 | 0.01 | 0.01 |
| | Control group | 58 | 0.04 | 0.01 | <0.001 | |

(BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight, SYL: Sylvian fissure area, TCD: Transcerebellar diameter, AO: Aortic valve diameter)

The difference in HC/SYL and AO/SYL ratios between the study and control groups was significant, and the results were similar to those for second-trimester fetuses. The HC/SYL ratios of 49 fetuses

in the study group and 58 fetuses in the control group were compared, with values of 2.71 ± 1.31 and 2.09 ± 0.49, respectively. The HC/SYL ratio was significantly higher in the CHD group compared to the control group ($p<0.001$).

In assessing the AO/SYL ratio, data from 36 fetuses in the study cohort and 58 fetuses in the control cohort were analyzed. The ratios were measured as 0.06 ± 0.04 in the CHDs group and 0.04 ± 0.01 in controls. Fetuses with CHDs demonstrated a significantly elevated AO/SYL ratio compared with healthy controls, consistent with findings observed in the second-trimester study cohort ($p = 0.01$).

Various classification systems for CHDs have been described in the literature. Jansen et al.[15] proposed a scheme based on oxygen saturation levels in the ascending aorta and hemodynamic flow patterns in the aortic arch. In this approach, ascending aortic oxygen saturation was used to classify CHDs into three categories: defects resulting in low-oxygen blood reaching the brain, conditions characterized by intracardiac mixing of oxygenated and deoxygenated blood, and defects in which oxygen-rich blood is preferentially delivered to the brain. According to the flow in the aortic arch, the classifications were defined as normal flow, restricted flow, and reversed flow. In the classification used by Clancy et al.[16], ventricular function and flow patterns in the aortic arch were considered. Using these two different classification systems, tables were constructed to compare the measurements of fetuses in the second- and third-trimester gestational age groups in the present study.

According to Jansen's[15] oxygen saturation classification, gestational ages did not differ between the study and control groups in any of the three categories. Although the mean BPD, HC, AC, FL, and EFW values tended to be lower in fetuses with reduced oxygen saturation and intracardiac mixing compared to those with normal oxygen saturation, these variations did not reach statistical significance ($p = 0.77$, 0.65, 0.17, 0.45, and 0.45, respectively).

The HC/EFW ratio and transcerebellar diameter measurements also presented no differences among the three groups ($p = 0.19$; 0.83). Although the mean values of the HC/SYL and AO/SYL ratios, as well as the Sylvian fissure area measurement, were larger in the low oxygen saturation group and smaller in the normal oxygen saturation group, however, these variations did not reach statistical significance ($p = 0.14$, 0.24, and 0.11, respectively).

The classification of fetuses with CHDs in our clinic and the comparison of their measurements are presented according to the aortic arch flow pattern classification proposed by Jansen et al.[15] There was no difference between the patient groups in terms of gestational age ($p = 0.71$).

When the mean values of BPD, HC, AC, FL, and EFW were examined in terms of biometric measurements of the fetuses, it was observed that there was no difference according to the flow pattern in the aortic arch (p values 0.39; 0.5; 0.6; 0.48; 0.55, respectively). HC/EFW, HC/SYL, and AO/SYL ratios, as well as transcerebellar diameter and Sylvian fissure area measurements, did not differ according to the aortic arch flow pattern ($p = 0.70$, 0.41, 0.60, 0.70, and 0.38, respectively).

In Table 3, the study group patients in the second trimester of pregnancy were classified according to the study conducted by Clancy et al.[16,] and their fetal measurements were compared.

According to this classification, the gestational ages of the patients included in the study were 22.45 ± 1.44 weeks for class 1, 21.67 ± 2.58 weeks for class 2, 21.73 ± 1.94 weeks for class 3, and 22.4 ± 1.43 weeks for class 4. No significant differences were found among the four groups in terms of gestational age ($p = 0.54$). Similarly, no differences were observed among the four groups with respect to BPD, HC, AC, FL, and EFW (p values: 0.24, 0.47, 0.39, 0.56, and 0.49, respectively). The HC/EFW and AO/SYL ratios, as well as transcerebellar diameter, also showed no significant differences among the groups (p values: 0.37, 0.34, and 0.46, respectively).

The HC/SYL ratio was found to be higher in class 2 and class 4 compared with the other groups, and this difference was statistically significant. When Sylvian fissure area measurements were compared, the highest value was observed in class 1 (60.11 ± 22.28 $mm^2$). This difference was also statistically significant compared with the other groups ($p = 0.04$).

**Table 3. Comparison of fetal measurements of patients diagnosed with second-trimester CHDs according to Clancy classification**

| Clancy classification | Value | GA | BPD | HC | AC | FL | EFW | HC/EFW | HC/SYL | TCD | SYL | AO/SYL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Biventricular no arch obstruction | Mean | 22.45 | 54.29 | 202.56 | 179.24 | 39.27 | 541.14 | 0.39 | 3.79 | 24.02 | 60.11 | 0.07 |
| | SD | 1.44 | 4.84 | 19.42 | 18.53 | 4.48 | 137.25 | 0.08 | 1.37 | 2 | 22.28 | 0.03 |
| Biventricular arch obstruction present | Mean | 21.67 | 51.43 | 193.88 | 174.15 | 36.68 | 494.33 | 0.43 | 6.28 | 24 | 37.7 | 0.09 |
| | SD | 2.58 | 7.64 | 32.75 | 27.97 | 7.03 | 194.23 | 0.11 | 2.3 | 3.75 | 20.91 | 0.03 |
| Single-ventricle no arch obstruction | Mean | 21.73 | 50.87 | 192.25 | 167.12 | 37.29 | 467.8 | 0.44 | 4.91 | 22.47 | 43.31 | 0.11 |
| | SD | 1.94 | 5.74 | 20.59 | 24.06 | 5.61 | 145.91 | 0.12 | 1.5 | 3.49 | 15.47 | 0.06 |
| Single-ventricle arch obstruction present | Mean | 22.4 | 54.12 | 201.71 | 177.19 | 38.85 | 524.1 | 0.4 | 5.05 | 23.41 | 44.1 | 0.09 |
| | SD | 1.43 | 5.19 | 18.77 | 16.98 | 4.44 | 130.16 | 0.07 | 1.67 | 2.77 | 16.32 | 0.05 |
| Total | Mean | 22.15 | 52.96 | 198.5 | 174.85 | 38.34 | 511.87 | 0.41 | 4.53 | 23.48 | 50.98 | 0.09 |
| | SD | 1.73 | 5.58 | 21.29 | 21.12 | 5.08 | 144.52 | 0.09 | 1.69 | 2.78 | 21.02 | 0.04 |
| p | | 0.54 | 0.24 | 0.47 | 0.39 | 0.56 | 0.49 | 0.37 | 0.02 | 0.46 | 0.04 | 0.34 |

GA: Gestational age, BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight, SYL: Sylvian fissure area, TCD: Transcerebellar diameter, AO: Aortic valve diameter, SD: Standard deviation)

Third-trimester patients with CHDs were compared according to the classification by Jansen et al.[13] based on oxygen saturation to the brain. The gestational age was 32.38 ± 2.38 weeks in the group with low oxygen saturation, 31.48 ± 2.64 weeks in the group with intracardiac mixing of oxygen-rich and oxygen-poor blood, and 30.64 ± 2.94 weeks in the group with normal oxygen saturation to the brain. No significant differences were observed among the third-trimester patient groups in terms of gestational age (p = 0.19).

No differences were observed among the three patient groups in terms of the mean values of the fetal biometric measurements BPD, HC, AC, FL, and EFW (p values: 0.19, 0.10, 0.39, 0.051, and 0.37, respectively). Similarly, no differences were found among these patient groups in terms of the HC/EFW, HC/SYL, and AO/SYL ratios, as well as transcerebellar diameter and Sylvian fissure area measurements (p values: 0.3, 0.51, 0.06, 0.12, and 0.52, respectively).

Fetal measurements of the third-trimester study group pregnancies were compared according to the aortic arch flow pattern classification. The gestational age was 32.78 ± 2.44 weeks in the group with a reversed aortic arch flow pattern, 31.14 ± 2.12 weeks in the group with restricted aortic arch flow, and 31.23 ± 2.70 weeks in the group with a normal flow pattern. No significant differences were observed among the groups in terms of gestational age (p = 0.10).

According to the aortic arch flow pattern, no significant differences were observed in fetal biometric measurements such as BPD, HC, FL, and EFW (p values: 0.22, 0.26, 0.74, and 0.07, respectively). However, AC measurements were larger in the group with reversed aortic arch flow compared with the groups with restricted and normal flow, and this difference was statistically significant (p = 0.04). Changes in the aortic arch flow pattern did not result in any differences among CHDs in terms of the HC/EFW, HC/SYL, and AO/SYL ratios or in transcerebellar diameter and Sylvian fissure area measurements (p values: 0.18, 0.74, 0.08, 0.56, and 0.53, respectively).

In Table 4, fetal measurements of third-trimester patients with CHDs were compared according to the classification applied in the study by Clancy et al.[16]. The mean gestational age was 31.06 ± 2.65 weeks for class 1, 33 ± 2 weeks for class 2, 31.85 ± 2.58 weeks for class 3, and 31.5 ± 0.96 weeks for class 4. Based on ventricular function and aortic flow, no significant differences were observed among the groups in terms of the mean values of BPD, HC, AC, FL, and EFW (p values: 0.28, 0.33, 0.25, 0.84, and 0.43,

respectively). Similarly, no significant differences were found among the groups for the HC/EFW and HC/SYL ratios, as well as transcerebellar diameter and Sylvian fissure area measurements (p values: 0.33, 0.39, 0.56, and 0.57, respectively). However, the AO/SYL ratio in class 1 was higher than in the other three groups, with a mean value of 0.08 ± 0.06 (p = 0.04).

**Table 4. Comparison of fetal measurements in third-trimester pregnancies with CHDs according to Clancy's classification**

| Clancy classification | Value | GA | BPD | HC | AC | FL | EFW | HC/ EFW | HC/SYL | TCD | SYL | AO/SYL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Biventricular. no arch obstruction | Mean | 31.06 | 78.11 | 287.28 | 272.96 | 60.01 | 1835.03 | 0.17 | 2.81 | 38 | 128.28 | 0.08 |
| | SD | 2.65 | 7.2 | 20.68 | 37.62 | 5.92 | 653.88 | 0.04 | 1.39 | 5.09 | 63.06 | 0.06 |
| Biventricular. arch obstruction present | Mean | 33 | 82.41 | 299.98 | 293.29 | 61.24 | 2112.75 | 0.15 | 1.99 | 40.45 | 154.75 | 0.03 |
| | SD | 2 | 6.02 | 14.19 | 30.92 | 4.28 | 485.13 | 0.03 | 0.45 | 4.64 | 39.33 | 0.01 |
| Single-ventricle. no arch obstruction | Mean | 31.85 | 78.81 | 293.98 | 275.59 | 59.59 | 1845.23 | 0.17 | 2.5 | 40.19 | 130.44 | 0.05 |
| | SD | 2.58 | 6.78 | 22.76 | 31 | 6.41 | 519.26 | 0.05 | 0.9 | 5.37 | 48 | 0.02 |
| Single-ventricle. arch obstruction present | Mean | 31.5 | 77.77 | 290.39 | 267.08 | 59.14 | 1744.86 | 0.18 | 3.1 | 38.52 | 113.74 | 0.04 |
| | SD | 2.96 | 6.87 | 24.9 | 33.28 | 7.37 | 578.98 | 0.05 | 1.73 | 5.64 | 51.02 | 0.02 |
| Total | Mean | 31.61 | 78.89 | 291.21 | 275.68 | 59.97 | 1865.63 | 0.17 | 2.71 | 38.97 | 129 | 0.06 |
| | SD | 2.64 | 6.93 | 21.14 | 34.95 | 6 | 591.46 | 0.04 | 1.31 | 5.16 | 55.1 | 0.04 |
| p | | 0.18 | 0.28 | 0.33 | 0.25 | 0.84 | 0.43 | 0.33 | 0.39 | 0.56 | 0.57 | 0.04 |

GA: Gestational age, BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight, SYL: Sylvian fissure area, TCD: Transcerebellar diameter, AO: Aortic valve diameter, SD: Standard deviation

## DISCUSSION

CHDs represent one of the most frequent congenital malformations. An underlying cause can be identified in approximately 15–30% of affected individuals. Both genetic predispositions and environmental influences contribute to their development. Although mortality associated with severe cardiac anomalies has steadily declined over recent years, complications such as growth restriction and neurodevelopmental difficulties are increasingly recognized[19].

Hypoxia and ischemia, in addition to growth restriction, are major causes of neurodevelopmental delay. Cerebral ischemia disrupts synapse formation in the fetus, leading to white matter damage by reducing the number of oligodendrocytes, and also leads to abnormalities in cortical development[20, 21].

It has been observed that as the survival time of these individuals increases, their neurological development in verbal, nonverbal, social, and academic areas lags behind their peers[22,23]. Although the neurodevelopmental failure experienced by children diagnosed with severe CHDs who survived for a long time was attributed solely to the surgery they underwent, studies conducted over the last three decades have shown that this process begins in the intrauterine period. Cerebral damage is observed in approximately 50% of newborns diagnosed with CHDs in the preoperative period[8, 24, 25]. Thus, neurodevelopmental delay in an individual with a severe CHD is the result of a complex process encompassing both the prenatal and postnatal periods, as well as the changes occurring within these stages.

When evaluating growth profiles, no significant differences were detected between the study and control groups regarding gestational age and fetal biometry in either the second or third trimester. The parameters used included oxygen saturation, flow pattern in the aortic arch, and ventricular function, which pump blood to the brain. Analyses conducted across three groups using two different classifications allowed for detailed hemodynamic subgroups within these patient groups. The results of this study will make an original contribution to the literature.

In the present study, comparison of second-trimester cases between the study and control groups demonstrated a significantly reduced Sylvian fissure area in the study cohort. This result suggests that cortical developmental abnormalities in fetuses with CHDs emerge prenatally and begin during the early phases of gestation[26, 27].

The development of cortical malformations can today be demonstrated by neuroimaging, even in the early stages of the intrauterine period. Monitoring the development of the Sylvian fissure, one of the dynamic changes occurring early in cortical surface development and maturation, represents a strong potential marker in this regard. In particular, the detection of abnormalities in Sylvian fissure development, considered a strong potential indicator for the early identification of cortical developmental disorders, is therefore of great importance[7]. In addition, studies have shown that the depth of the Sylvian fissure is more pronounced in CHDs that cause limited left cardiac flow, compared to the control group fetuses[28].

In the second-trimester cohort, when classified according to oxygen saturation and aortic arch flow characteristics, fetal biometric parameters did not show any statistically significant differences. However, in the classification proposed by Clancy et al.[16], the Sylvian fissure area measurement was highest in patients with biventricular function and normal aortic flow. In other words, in class 1 patients with CHDs, who are hemodynamically closest to normal, oxygenation and normal aortic flow differed in terms of Sylvian fissure development compared with classes 2, 3, and 4 (Table 3).

Cardiac anomalies with two functional ventricles and no obstruction in the aortic arch represent the group with the least cerebral oxygen deficiency, and in this group, the fetal Sylvian fissure area measurement showed a statistically significant difference ($p = 0.04$). A recent study reported that in fetuses with CHDs, particularly those at risk of moderate-to-severe cerebral oxygen deficiency, Sylvian fissure depth was significantly smaller compared with the control group[27]. This finding suggests that cortical development is delayed or adversely affected. In particular, gyral sulcal structures expected to develop by the 33rd week of gestation (such as the Sylvian fissure) have been shown to be shallower, shorter, and less convoluted in the presence of CHDs[18, 30]. The study emphasizes that such sulcal development findings may be early markers of neurodevelopmental effects in the intrauterine period, as in our study.

Recent evidence indicates that infants with hypoplastic left heart syndrome tend to have smaller head circumferences, while other biometric parameters remain comparable to those of infants without CHDs[9].

In our analysis, stratification by aortic arch flow characteristics and ascending aortic oxygen saturation did not reveal any significant differences in Sylvian fissure area ratios among patients in the second and third trimesters. In the study by Jansen et al.[15], fetuses with CHDs were evaluated by comparing cerebral structures both volumetrically and through Sylvian fissure depth measurements with the control group. In the assessment based on oxygen saturation, the group with abnormal oxygen saturation was found to have smaller brain volumes compared with the group with normal oxygen saturation. However, in the grouping based on aortic arch flow, no volumetric differences were observed [31]. In the 2025 study by Xiong et al.[32], HC measurements in fetuses with CHDs were found to be smaller, particularly in the second-trimester group. As gestational age advanced, the reduction in HC more pronounced in the early stages was observed to gradually approach normal values.

Wallenstein et al.[33] showed that fetuses with CHDs experience altered hemodynamics from early development, and depending on the defect type, have a three-fold increased risk of growth restriction compared to healthy controls. Among fetal biometry parameters, HC is particularly affected in individuals with CHDs at risk for intrauterine growth restriction (IUGR). Research indicates that fetuses with hypoplastic left heart syndrome display abnormal and disproportionate head circumference growth, whereas normal fetuses typically show proportional HC growth after mid-gestation[34]. In the present study, head circumference measurements did not differ significantly between the study and control groups during either the second or third trimester. In fetuses with CHDs, the delay in Sylvian fissure development an early marker of neurodevelopmental delay was demonstrated in this study through the HC/SYL ratio, consistent with previous findings. The elevated HC/SYL ratio in CHD fetuses supports the hypothesis of delayed cortical maturation and suggests that proportional neurosonographic indices may serve as sensitive prenatal markers of impaired cortical development in this high-risk population.

Furthermore, while HC measurements in fetuses with CHDs have shown heterogeneity across multiple studies, the HC/SYL ratio was found to differ significantly from the control group, regardless of gestational age[32]. This supports the usability of the parameter.

As a hemodynamic parameter, the ratio of the aortic valve measurement to the Sylvian fissure area a potential indicator of cortical development and its significant difference in fetuses with CHDs represent one of the key measures demonstrating the impact of CHDs on cortical development, further indicating that hemodynamics are closely related to cortical development[34, 35].

Two studies evaluating fetal brain volumes in CHD cases versus controls demonstrated that cardiac diagnosis and the proportion of combined ventricular output through the aortic valve were independently linked to total brain volume and thus cerebral development[31, 36].

In this study, based on the classification by Clancy[16] for the second-trimester study group, the HC/SYL ratio was observed to be significantly elevated in the patient groups with restricted aortic flow patterns (classes 2 and 4). Although no statistical difference was observed for HC in this patient group, it was demonstrated consistent with the literature that one of the determining factors affecting Sylvian fissure development, and thus altering the ratio, is adequate aortic flow. This is because the percentage of outflow through the aortic valve is an independent factor influencing volumetric brain development and, consequently, cortical folding and maturation.

In our study, according to the classification by Jansen et al.[15], in the third-trimester patient group, AC was found to be significantly larger in patients with reversed flow in the aortic arch. However, given that CHDs are linked to altered hemodynamics and therefore carry an inherent risk of IUGR, this parameter was excluded from further consideration.

In the third-trimester patient group, according to the classification by Clancy et al.[16], no significant differences were detected in Sylvian fissure area measurements among the study group patients. As expected, however, the AO/SYL ratio was found to be significantly higher in the group with normal aortic flow and two functional ventricles. In the class 1 group, which exhibits hemodynamics closest to normal, greater aortic flow and more effective ventricular function compared with the other groups, explains the higher ratio, a finding consistent with the literature[34].

Although third-trimester Sylvian fissure measurements did not significantly differ between the study and control groups, the proportional data described above suggest that cortical developmental delay continues. The use of such ratios is important, as they reduce the heterogeneity of single measurements dependent on gestational age. In this context, the HC/SYL and AO/SYL ratios can serve as distinctive parameters in the routine prenatal follow-up of fetuses with CHDs for neurologic monitoring related to hemodynamics. These ratios can provide a novel contribution to the literature by facilitating the evaluation of the relationship between cortical development and fetal hemodynamics, although their clinical and prognostic utility requires further validation with postnatal outcome data.

Several limitations of this study should be acknowledged. First, the retrospective single-center design may limit the generalizability of the findings and may have introduced selection bias. Second, comprehensive genetic testing was not available for all cases, and some potentially relevant maternal variables, such as body mass index, smoking status, and parity, were not consistently available in the control group. Third, formal inter-observer variability analysis could not be performed because of the retrospective nature of the study. Finally, postnatal neurodevelopmental follow-up data were not available. Therefore, the clinical and prognostic implications of these prenatal neurosonographic findings should be interpreted with caution and require further confirmation in prospective studies.

Neurodevelopmental abnormalities are common in newborns and children prior to surgery. The presence of these abnormalities indicates pre-existing brain injury during the antenatal or early postnatal period, independent of surgery.

The prenatal identification of fetuses diagnosed with CHDs and the evaluation of their growth and neurodevelopmental status are important for informing parents and ensuring early multidisciplinary management after birth. Early diagnosis and planned treatment contribute both to the survival of individuals with CHDs and to the preservation of their existing neurological status[37].

The use of specific parameters (particularly the Sylvian fissure) has been considered promising for the assessment of neurodevelopment. The study by

Welling et al. demonstrated that Sylvian fissure measurements may be associated with neurodevelopmental outcomes at 2 years of age[27]. Similarly, INTERGROWTH-21st data reported that fetuses with assessed Sylvian fissure maturation showed adequate growth and development at 2 years[13]. Although normal Sylvian fissure development appears to be consistent with normal neurodevelopment, its prognostic value as an indicator of developmental problems has not yet been definitively established.

In conclusion, previous studies have shown that in fetuses with CHDs, particularly those with left ventricular outflow tract obstruction and impaired forward aortic flow, white matter and cortical development are delayed[21]. This indicates that the processes affecting neurological development in the postnatal period actually begin during the prenatal stage[36]. In prenatal follow-up, the type of CHDs, hemodynamic factors, and neurological development are only some of the variables that influence postnatal management. Particularly in diagnoses originating from left cardiac dysfunction, CHDs represent a complex health condition that begins in the prenatal period and is further influenced by preoperative, perioperative, and postoperative conditions and associated risk factors. As demonstrated in our study, the early detection of cortical developmental delay is important both for informing the families of these fetuses and supporting the early identification of potential postnatal neurodevelopmental risk. In this regard, rather than relying on a single measurement parameter, the use of combined ratios such as HC/SYL and AO/SYL which integrate growth and hemodynamic parameters to overcome existing heterogeneity will be more informative. With advancing technology and ongoing innovations, CHDs can be identified at earlier gestational ages, and new studies in this field incorporating growth parameters together with hemodynamic indices for the monitoring of cortical development will further elucidate this process.

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