Original Article

Comparison of Cerebral Blood Circulation of Fetuses with Congenital Heart Disease with Healthy Fetuses

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Abstract

Background: The effect of congenital cardiac malformation on fetal cerebral circulation has not been well known. This study aimed to compare the cerebral blood circulation of fetuses with congenital heart disease (CHD) with healthy fetuses. **Methods:** This prospective cohort study included 37 pregnant women who presented to the gynecology and obstetrics department of department of Farabi Hospital, Faculty of Medicine, Karadeniz Technical University for anomaly screening in the second trimester. The women were divided into two groups as those with fetuses having CHD and healthy fetuses. Middle cerebral artery (MCA), peak systolic velocity (PSV), pulsatility index (PI), resistivity index (RI), systole/diastole (S/D) ratio, and MCA transverse section diameter (mm) were recorded for each fetus. **Results:** The most common CHDs were truncus arteriosus and hypoplastic left heart syndrome. The mean MCA PSV, resistivity index, and MDCA vessel diameter values were statistically significantly higher in the study group compared with fetuses without CHDs. The mean PI and systole/diastole ratio were statistically significantly lower in the study group than in the control group. **Conclusion:** This study reported that MCA PSV, RI, and vessel diameter were significantly higher and the S/D ratio and PI were significantly lower in fetuses with CHD compared to the healthy fetuses.

Keywords: Congenital heart disease, Doppler ultrasonography, middle cerebral artery, pulsatility index, resistivity index

Introduction

Congenital heart disease (CHD) consists of a wide spectrum of anomalies and malformations involving the heart and great vessels that occur during the development of the cardiovascular system *in utero* and is one of the most common birth defects.[1] CHD is associated with a high perinatal, long-term morbidity and mortality and is seen in approximately 0.4%–1.3% of live newborns.[2]

Intrauterine diagnosis of CHD is extremely important. In a recent systematic review, the rate of prenatal detection was reported as 45.1%.[3] Since there is an increased risk of developing CHD in the next child, it should be questioned whether there is a history of a child with CHD from the mother's previous birth history and risk factors should be investigated. These risk factors include type and severity of defect and presence of a genetic syndrome. CHD presented in approximately 80% of patients with Noonan syndrome, although it had a low risk of recurrence since it was sporadic.[4]

CHD is important not only for neonatal death but also for neonatal neurological development. Neurological and developmental dysfunctions are common extracardiac complications in CHD.[5] Studies have found abnormal cerebral blood flow in fetuses with CHD.[6] Recent study has demontrated that altered brain development as early as the fetal period is a major cause of worse neurocognitive outcomes in CHD.[7] In fetal anomaly screening, cerebral blood flow is measured by Doppler ultrasonography. In these studies, pulsatility index (PI) and resistivity index (RI) parameters were examined in the Doppler ultrasonographic examination performed on the middle cerebral artery (MCA).[8]

The objective of this study was to compare the cerebral blood circulation of fetuses with CHD followed in current clinic with healthy fetuses.

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Received: 01-06-2023 **Revised:** 13-09-2023 **Accepted:** 26-10-2023 **Available Online:** 26-02-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_66_23

How to cite this article: Patir MG, Guven ESG, Albayrak M, Guven S. Comparison of cerebral blood circulation of fetuses with congenital heart disease with healthy fetuses. J Med Ultrasound 2024;32:329-33.

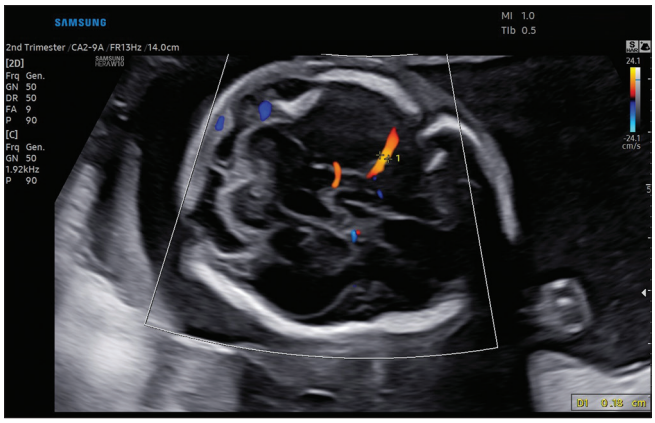

Figure 1: Axial view measuring the middle cerebral artery diameter

Materials and Methods

The study protocol was approved by the local ethics committee of current university hospital (date December 16, 2019, number 2019/348). Patients were informed about the objective and procedure of the study and gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki revised in 2013.

Study design

This prospective cohort study included 40 pregnant women who presented to the gynecology and obstetrics department of current hospital for anomaly screening in the second trimester (gestational weeks between 18 and 28). Pregnant women aged 18–35 years with single pregnancy in the second trimester who presented to the obstetrics outpatient clinic for routine follow-up without any complaint and referred for further investigations due to suspected or diagnosed CHD were assigned to the study group (n = 16). Control group consisted of pregnant women aged 18–35 years with single pregnancy in the second trimester who presented to the obstetrics outpatient clinic for routine follow-up without any complaint (n = 21). Renal, hepatic, and thyroid functions were normal in all pregnant women.

Patient selection

All cases who presented consecutively between study years were evaluated in terms of inclusion criteria and accepted to the study in the order of their presentation to the obstetrics outpatient clinic. In this context, the first 40 cases who presented to the outpatient clinic were included in the study. The exclusion criteria were as follows: (i) a history of endocrinopathy (including diabetes mellitus, hyperprolactinemia, Cushing's disease and congenital adrenal hyperplasia), a systemic disease (e.g., asthma), a collagen disorder, hypercholesterolemia, sickle cell anemia or neoplasm; (ii) Patients with a history of coronary artery disease, angina or myocardial infarction, or any known history of vascular, infectious, or inflammatory disease, patients with hypertension, history of coronary arteritis, and electrocardiographic changes, maternal autoimmune disease; (iii) Use of any medication (e.g., insulin-sensitizing drugs, oral contraceptives, antiandrogens, statins, aspirin, corticosteroids) within 3 months before pregnancy; (iv) Multiple fetuses pregnancy; (v) Current smoking; (vi) Refuse to participate in the study; (vii) Rh incompatibility; (viii) Having other structural anomalies other than heart disease for the study group; (ix) Abnormal aneuploidy screening/diagnosis (double, triple test, free fetal DNA test, chorionic villus sampling, amniocentesis); (x) Having abnormal uterine (Elevated resistance indices (95th percentile for gestational age as the threshold for abnormal uterine artery doppler) and/or persistent uterine artery notching) and/or umbilical (absence or reverse end diastolic flow or umbilical artery PI (>95 thpercentile))[9] arteries Doppler findings. Three patients with exclusion criteria were excluded and the study was completed with 37 pregnant women. The pregnant women were included in the study after they signed the informed consent form and it was determined that they volunteered to participate in the study.

Middle cerebral artery measurement and data collection

An axial section with the fetal head in the transverse plane was obtained. An axial section of the brain, including the thalami and the sphenoid bone wings, was visualized and magnified. The MCA vessels were found with color or power Doppler ultrasound overlying the anterior wing of the sphenoid bone near the base of the skull. The reading was obtained close to its origin in the internal carotid artery. An angle of insonation of <15° was used. MCA peak systolic flow (PSF), PI = (Systole-Diastol)/Mean flow, resistivity index (RI = [Systole-Diastol]/Systole), systole/diastole (S/D) ratio and MCA transverse section (mm) were recorded for each fetus [Figure 1]. Doppler examinations were performed by the same researcher (ESGG) using the VOLUSON E-10 ultrasonography device. The diagnosis of CHD was carried out by 2-dimensional and Doppler ultrasonography.

Age, gravida, parity, biparietal diameter, abdominal circumference, femur length, and estimated birth weight (EFW) data for each fetus in the second trimester were recorded for all participants. MCA PSF, PI = (Systole-diastol)/Mean flow, resistivity index (RI = [Systole-Diastol]/Systole), S/D ratio and MCA transverse section (mm) were recorded for each fetuses [Figure 1]. Doppler examinations were performed by the same researcher (ESGG) using the VOLUSON E-10 ultrasonography device. The diagnosis of CHD was confirmed by postnatal 2-dimensional and Doppler ultrasonography.

Statistical analysis

Data obtained in this study were statistically analyzed using the SPSS version 24.0 (SPSS, Statistical Package for the Social Sciences, IBM Inc., Armonk, NY, USA). Normality of the variables was tested using the Kolmogorov–Smirnov test. As the variables were nonnormally distributed, the Mann–Whitney test among the nonparametric tests was used in comparison of the variables between the groups. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were given as number and percentage (n, %). P <0.05 was considered statistically significant.

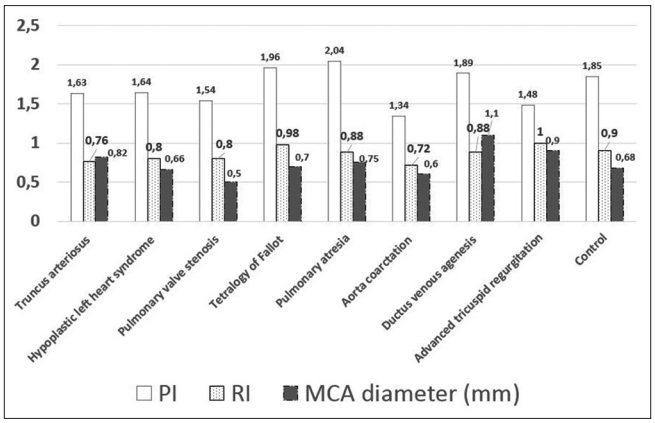

Figure 2: The mean values of pulsatility index/resistivity index/middle cerebral artery diameter (mm) in different congenital heart diseases. MCA: Middle cerebral artery; PI: Pulsatility index; RI: Resistivity index

Results

The mean age of all participants was 29.27 ± 4.31. The mean gravida number was 2.35 ± 1.55 and the mean parity number was 1.05 ± 1.17. Demographic data and ultrasonographic measurements of all participants are given in Table 1.

Distribution of CHDs in the study group was truncus arteriosus (32%), hypoplastic left heart syndrome (32%), pulmonary valve stenosis (6%), tetralogy of Fallot (6%), pulmonary atresia (6%), aorta coarctation (6%), ductus venous agenesis (6%), and advanced tricuspid regurgitation (6%).

Table 2 shows the comparison of demographic and ultrasonographic data between the CHD and control groups. The mean MCA peak systolic velocity (PSV), RI, and MCA vessel diameter (mm) values were statistically significantly higher in the study group compared with fetuses without CHDs. The mean PI and systole/diastole ratio were statistically significantly lower in the study group than in the control group. The mean values of PI/RI/MCA diameter (mm) in different CHDs are given in Figure 2.

Table 1: Demographic data and ultrasonographic measurements of all participants

Demographic/ultrasonographic data	Mean±SD
Age (years)	29.27±4.31
Gravida (*n*)	2.35±1.55
Parity (*n*)	1.05±1.17
Gestational week	22.23±3.38
Fetus EFW (g)	752.30±365.08
MCA PSV (cm/s)	30.13±5.09
PI (ratio)	2.01±0.78
RI (ratio)	0.93±0.38
MCA vessel diameter (mm)	0.83±0.27
S/D ratio	5.07±1.74

EFW: Estimated fetus weight, MCA: Middle cerebral artery, PSV: Peak systolic velocity, PI: Pulsatility index, RI: Resistive index, S/D: Systole/diastole, SD: Standard deviation

Table 2: Comparison of demographic and ultrasonographic data between groups

Parameter	CHD group (*n*=16)	Control group (*n*=21)	*P*
Age (years)	30.37±4.05	28.43±4.41	0.229
Gravida (*n*)	2.50±1.46	2.24±1.64	0.439
Prity (*n*)	1.19±1.22	0.95±1.16	0.554
Gestational week	31.01±5.88	29.98±4.22	0.575
Fetus EFW (g)	22.89±3.58	23.50±3.28	0.728
MCA PSV (cm/s)	33.20±4.50	27.79±4.27	<0.001
PI	1.41±0.26	2.47±0.74	<0.001
RI	1.19±0.43	0.73±0.15	<0.001
MCA diameter (mm)	1.07±0.20	0.67±0.16	<0.001
S/D	4.40±2.45	5.52±0.61	0.018

Mann–Whitney *U*-test was used for comparison. EFW: Estimated fetus weight, MCA: Middle cerebral artery, PSV: Peak systolic velocity, PI: Pulsatility index, RI: Resistivity index, S/D: Systole/diastole, CHD: Congenital heart disease

Discussion

In this study, we examined the MCA vessel diameter, PI, PSV, resistive index (RI), and S/D ratio in fetuses with CHD and healthy fetuses. The resistance of blood flow in a vessel is determined by three factors including blood viscosity, the length, and diameter of the vessel. The most important parameter is vessel diameter. Since vessel length is constant and changes in blood viscosity are slight, the most variable parameter is vessel diameter.[10] Therefore, we also measured the MCA vessel diameter in our study.

In the studies in the literature, the brain sparing effect in fetuses with intrauterine growth restriction (IUGR) was defined according to the MCA flow velocity.[11] In a study conducted by Barzilay *et al*. in 2015, twin fetuses with IUGR were evaluated and no significant correlation was found between increased MCA diameter and perinatal outcome.[12] However, in that study, vessel diameter was not measured directly. We directly measured vessel diameters in fetuses with CHD and healthy fetuses in singleton pregnancies. MCA diameter was found to be statistically significantly higher in fetuses with CHD than in healthy fetuses ($P < 0.001$). MCA vessel diameter may be a parameter to evaluate cerebral blood flow in fetuses with CHD. However, more studies on vessel diameter are needed.

In an autopsy study by Gielecki *et al*. in 2009, MCA vessel diameter was measured in 152 fetal brains with a gestational age of 12–40.[13] The mean data on the development of MCA by weeks of gestation were found to be almost the same as the mean data in healthy fetuses in our study. In the same study, the vessel diameter was directly measured, and the vessel may be difficult to visualize on ultrasonography and there may be a margin of error of ± 1 mm in the measurements. In our study, we evaluated the MCA vessel diameter by ultrasonographic method. In the present study, live and intrauterine fetuses were included, and the mean vessel diameter of healthy fetuses gave similar results with the above-mentioned study,

suggesting that it is possible to measure the MCA vessel diameter intrauterine.

In many studies, MCA PI values of fetuses with CHD have been compared with healthy fetuses. MCA PI values were found to be statistically significantly higher in healthy fetuses.[14-16] In our study, similar to these studies, the MCA PI value of fetuses with CHD was found to be statistically significantly lower compared to healthy fetuses.

Our study is the first in the literature to investigate the MCA PI, PSV, RI (resistive index), and S/D ratio in fetuses with CHD. There are studies conducted on healthy fetuses. In one study, 2323 singleton pregnant women between 19 and 41 weeks of gestation were examined. In our study, the mean value of MCA PSV was found as 27.79 ± 4.27 in the control group. This value corresponds to the 5–10th percentile value in the study by Morales-Roselló *et al*.[17] Our study was consistent with this study. In our study, MCA PSV was found to be higher when normal values were compared with fetuses with CHD, and the difference was statistically significant. Since there is no other study in the literature, MCA PSV can be used as a parameter when evaluating the cerebral circulation of fetuses with CHD.

In our study, we found the mean MCA RI value as 0.73 ± 0.15 in the control group. In a study by Tarzamni *et al*., MCA nomograms of fetuses in Iran were compared with other countries and found to be lower.[18] However, they obtained similar results with other countries in the parabola curve. When compared with this study, our MCA RI rate was found to be consistent with the mean values between 24 and 28 weeks.

In our study, the mean S/D ratio was found to be 5.52 ± 0.61. Although there are ethnic and geographical differences, MCA RI and S/D levels at the same gestational week were found to be similar in the aforementioned study. S/D ratio was found to be lower in fetuses with CHD compared to healthy fetuses ($P = 0.018$). Thus, this ratio can be used as a parameter for cerebral circulation in fetuses with CHD.

In the present study, the most common CHD was truncus arteriosus in five patients, followed by hypoplastic left heart syndrome in five patients, and tricuspid regurgitation, ductus venosus agenesis, aortic coarctation, pulmonary atresia, tetralogy of Fallot and pulmonary valve stenosis in each one patient. In a recent study, the most common CHD was pulmonary valve abnormalities/noncritical pulmonary stenosis, followed by balanced atrioventricular canal defects, and left ventricular outflow tract obstruction/aortic valve abnormality/coarctation/interrupted aortic arch.[19] The difference in the number of CHDs was attributed to the number of patients included in the studies, although similar CHDs were found in our study.

In fetal CHDs, there is usually an anatomical disorder and the normal anatomy of the heart is disrupted. Since there is a placental circulation in the pregnant uterus, it prevents serious fetal effects. However, due to the cardiac anomaly that exists after birth, the fetal circulation and hemodynamics are disrupted, all systems are affected, and a process leading to the death of the newborn may occur. According to our research results, fetal heart anatomical disorder probably causes inadequate or deficient blood supply and oxygenation in the brain. The most important evidence of this situation is the increase in MCA PSV, just like in fetal anemia. In addition, since brain oxygenation disorder affects the development of the fetus, babies with fetal CHD are born with low birth weight. This hypothesis is supported by the low MCA PI value, just like in fetal IUGR. Unfortunately, since there is no research on this subject in the literature, it is not possible to support our hypothesis with literature data. However, future large-series prospective studies will support this hypothesis.

In our study, we found no significant difference in demographic parameters (age, EFW, number of pregnancies, parity number, and gestational week) with the control group ($P > 0.05$). In a study by Zeng *et al*.,[20] no significant difference was found in demographic parameters, like our study. Our study was compatible with the literature. We concluded that cerebral circulation in fetuses with CHD was not affected by demographic parameters such as age, parity, and number of pregnancies.

Major limitation of this study is the relatively small number of patients. Strengths of this study include the measurements to be made by the same researcher, easy to apply, not requiring additional costs, and its prospective design. In addition, additional visits were not needed because the examination could be performed during routine controls.

Conclusion

This study reported that MCA PSV, RI, and vessel diameter were significantly higher and the S/D ratio and PI were significantly lower in fetuses with CHD compared to the healthy fetuses. Examining these parameters in fetuses with CHD in early intrauterine period may predict early diagnosis for postnatal neurodevelopmental interventions. However, further studies with a larger series of patients are needed to support our findings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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