The Investigation of Cerebroplacental Ratio and Some Cranial Biometric Measurements in Fetuses with Isolated Congenital Heart Disease

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ABSTRACT

Objective: In this study, we aimed to compare the measurements of some fetal cranial structures and Doppler parameters between the groups with congenital heart disease and healthy pregnant women.

Materials and Methods: The study included 30 patients with intrauterine congenital heart disease and 30 healthy pregnant women. Fetuses with additional structural and genetic abnormalities were excluded from the study. In both groups, biparietal diameter (BPD), head circumference (HC), transcerebellar diameter (TCD), middle cerebral artery pulsatility index (MCA-PI), umbilical artery pulsatility index (UA-PI), umbilical artery resistance index (UA-RI), and umbilical artery systole/diastole ratio (UA S/D), as well as superior-inferior diameter of the cavum septum pellucidum (CSP) were measured by ultrasound. The cerebroplacental ratio (CPR), which is an indicator of the protective effect on the brain, was calculated. Data were statistically compared between the two groups, and $P < 0.05$ was considered statistically significant.

Results: A statistically significant difference was found between the groups in UA-RI and UA S/D values. The UA-RI and UA S/D values were significantly higher in the patient group than in the control group ($P=0.048; P < 0.001$). HC values were lower in the congenital heart disease group, and this result was statistically significant ($P=0.047$). There was no statistically significant difference between groups in BPD, HC, and TCD Z-scores. There was no statistically significant difference between groups in MCA-PI < 5th percentile, UA-PI > 95th percentile, and CPR < 1 scores.

Conclusion: Congenital heart disease may cause chronic fetal hypoxia during the intrauterine process and lead to changes in the fetomaternal circulation. This study suggests that there may be relationships between fetal cranial biometric retardation and cerebral perfusion changes.

KEYWORDS
Congenital heart defects; fetal hypoxia; doppler; fetal brain.

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**Introduction**

Congenital heart disease (CHD) is among the most common congenital anomalies and occur with a frequency of about 0.6-1%.\(^1\) They are emerging as an important cause of mortality and morbidity in children. Although advances in early diagnosis and postnatal management are increasing survival rates, neurodevelopmental disorders represent a major long-term problem.\(^2\)\(^-\)\(^6\)

Originally, neurodevelopmental disability was thought to be related to brain injuries that may result from postnatal surgical procedures and supportive care protocols. However, recent studies have shown that infants have brain damage and decreased biometric measures on magnetic resonance imaging performed before surgery.\(^7\)\(^-\)\(^9\)

This suggests that intrauterine exposure may also contribute to poor long-term outcome.

It is known that in a normal physiologic intrauterine process, mechanisms are active that conduct nutrient-rich blood from the placenta and systemic vasculature to vital organs such as the brain. In pathological conditions such as placental insufficiency, which may be associated with hypoxia, cardiac and vascular adaptive mechanisms are activated to maintain fetal cerebral perfusion, which is termed the “brain sparing effect”.\(^10\) It is hypothesized that, similar to placental insufficiency, the adaptive mechanisms by which altered brain perfusion may occur in fetuses with CHD are inadequate, which may contribute to abnormal neurodevelopment. In addition, brain damage in CHD patients is thought to be present at birth and is due to chronic cerebral hypoxia caused by direct administration of deoxygenated blood or intracardiac mixing of oxygenated and deoxygenated blood during the fetal period. During hypoxia, there is a redistribution of blood flow to the brain, which can be detected by Doppler measurement of the lower resistance index (RI) of the middle cerebral artery (MCA) and the higher RI of the umbilical artery (UA).\(^10\)

A relationship between fetal head circumference and Doppler examination has been found in fetuses with CHD.\(^11\) Studies have shown that abnormal head circumference may be associated with decreased brain perfusion and hypoxia.\(^12\)\(^-\)\(^14\)

In our study, we examined the biometric measurements of some fetal cranial structures in fetuses with congenital heart defect and the Doppler parameters used to assess Cerebroplacental flow and compared them with healthy pregnant women, based on the knowledge that cardiac output may contain different amounts of deoxygenated blood because of shunts that form between the cardiac cavities.

**Material and Methods**

This prospective case-control study was conducted in the Department of Perinatology, Dr. Zekai Tahir Burak Women’s Health Training and Research Hospital, Ankara, Turkey between December 2018 and February 2019. The protocol of this study was approved by the Ethics Committee of the hospital, written informed consent was obtained from each participant, and the study was conducted based on the universal ethical principles of the Declaration of Helsinki.

A total of 60 pregnant women participated in the study, 30 of whom were diagnosed with congenital heart disease (CHD) and 30 healthy pregnant women of the same gestational age served as the control group. Power analysis performed with the G_Power 3.0.10 program showed that at least 60 samples with an effect size of \(d = 0.5\), a margin of error of 5%, and a power of 80% were sufficient (\(n_1=30\), \(n_2=30\)). Pregnant women in both groups were between 28 and 40 weeks’ gestation in the third trimester of pregnancy. Data including demographic and clinical characteristics were obtained from medical records. Gestational age was confirmed by sonographic measurements of crown-rump length.
in the first trimester. Exclusion criteria included coexisting chronic systemic diseases, gestational diabetes, chromosomal abnormalities or other congenital anomalies, multiple pregnancies, pregnancy complications such as fetal growth restriction, and gestational diabetes mellitus.

Fetal ultrasonographic and echocardiographic assessment and Doppler measurements were performed transabdominally using a Ge Volusion 730 Expert sonography unit with a 3.5-MHz curved transducer by a single fetal and maternal medicine specialist with 10 years of experience. Fetal biometric measurements and Doppler parameters such as biparietal diameter (BPD), head circumference (HC), middle cerebral artery (MCA), and umbilical artery (UA) were performed according to the guidelines of the Institute of Ultrasound in Medicine and the International Society of Ultrasound in Obstetrics and Gynecology at the time of diagnosis of CHD. Cerebroplacental ratio (CPR) was determined by dividing the MCA pulsatility index (MCA-PI) by UA pulsatility index (UA-PI). Transcerebellar diameter (TCD) and superior inferior length of the cavum septum pellucidum (CSP) were measured in transcerebellar axial section.

Data for statistical analyzes were analyzed using IBM SPSS Statistics 21.0 (IBM Corp. Armonk, NY). The Kolmogorov-Smirnov test was used to assess the status of the data distributions. Numerical variables were expressed as standard deviation and mean. Measured values for BPD, HC, and TCD were converted to Z scores based on published normative data. Comparison of statistical significance between two independent groups according to their distribution ranges was performed using the parametric t-test for independent samples and the nonparametric Mann-Whitney U test. P-values below 0.05 were considered statistically significant.

Results

The demographic and clinical characteristics of the study groups are shown in Table 1. There were no differences between the study groups in maternal age, gravidity, parity, abortion, BMI, and gestational age during ultrasonographic examination ($P=0.157$, $P=1.000$, $P=0.977$, $P=0.819$, $P=0.158$, $P=0.793$ respectively).

The Doppler and some cranial parameters of both groups are shown in Table 2. Significant differences were found from the point of umbilical artery systole and diastole ratio, umbilical artery resistance index ($p < 0.001$, $P=0.048$, respectively). Compared with the control group, higher umbilical artery RI and S/D were found in the CHD group. There were no statistically significant differences between groups in middle cerebellar artery pulsatility index and umbilical artery pulsatility index ($P=0.076$, $P=0.148$). For fetal cranial parameters, HC was statistically lower in the CHD group compared to the control group ($P=0.047$). Statistically significant differences were not detected in terms of BPD, TCD, CSP between groups ($P=0.456$, $P=0.242$, $P=0.494$, $P=0.096$, respectively).

Table 3 shows the comparison of fetal cranial biometry scores according to the Z-score. There were no statistical differences in BPD (Z-score), HC (Z-score), TCD (Z-score) between the CHD group and the control group ($P=0.448$, $P=0.052$, $P=0.369$, respectively).

The relationship of some Doppler parameters between the groups was shown in Table 4. Participants in the two groups had no significant differences, including MCA-PI < 5 percentile, UA-PI > 95 percentile, and CPR < 1. ($P=0.624$, $P=0.227$, $P=0.337$ respectively).
Table 1: Demographic characteristics of the study group

<table>
<thead>
<tr>
<th></th>
<th>CHD group (n= 30)</th>
<th>Control group (n= 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28,0 [19-40,0]</td>
<td>27,0 [18,0-42,0]</td>
<td>0,157</td>
</tr>
<tr>
<td>Gravida</td>
<td>2,0 [1,0-6,0]</td>
<td>2,0 [1,0-6,0]</td>
<td>1,000</td>
</tr>
<tr>
<td>Parity</td>
<td>2,0 [1,0-6,0]</td>
<td>1,0[0,0-4,0]</td>
<td>0,977</td>
</tr>
<tr>
<td>Abortus</td>
<td>0,0 [0,0-3,0]</td>
<td>0,0 [0,0-3,0]</td>
<td>0,819</td>
</tr>
<tr>
<td>BMI* (kg/m2)</td>
<td>31,65±5,57</td>
<td>29,30±5,24</td>
<td>0,158</td>
</tr>
<tr>
<td>Gestational age at assessment (weeks)</td>
<td>32,0 [28,0-40,0]</td>
<td>32 [28,0-39,0]</td>
<td>0,793</td>
</tr>
</tbody>
</table>

*Body mass index

*Note: Data are expressed as mean, standard deviation, median (minimum-maximum), or number where appropriate. P Value < 0.05 indicates significant difference.

Table 2. Comparison of Doppler parameters and some cranial structures between groups

<table>
<thead>
<tr>
<th></th>
<th>CHD group (n= 30)</th>
<th>Control group (n= 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA S/D*</td>
<td>3,47±0,72</td>
<td>2,54±0,37</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>UA-PI*</td>
<td>1,03±0,30</td>
<td>0,96±0,37</td>
<td>0,148</td>
</tr>
<tr>
<td>UA-RI*</td>
<td>0,71±0,35</td>
<td>0,61±0,09</td>
<td>0,048</td>
</tr>
<tr>
<td>MCA-PI*</td>
<td>1,58±0,47</td>
<td>1,96±0,73</td>
<td>0,076</td>
</tr>
<tr>
<td>HC*</td>
<td>283,0 [213,0-340,0]</td>
<td>305,5 [266,0-350,0]</td>
<td>0,047</td>
</tr>
<tr>
<td>BPD*</td>
<td>78,5 [64,0-91,0]</td>
<td>80,5 [65,0-93,0]</td>
<td>0,456</td>
</tr>
<tr>
<td>TCD*</td>
<td>36,5 [31,0-50,0]</td>
<td>40,0 [30,0-52,0]</td>
<td>0,242</td>
</tr>
<tr>
<td>CSP*</td>
<td>5,30±1,55</td>
<td>4,64±1,33</td>
<td>0,096</td>
</tr>
</tbody>
</table>


*Body mass index

*Note: Data are expressed as mean, standard deviation, median (minimum-maximum), or number where appropriate. P Value < 0.05 indicates significant difference.
Table 3: Comparison of Fetal Cranial Biometry Values according to Z score

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHD group (n= 30)</th>
<th>Control group (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD&lt;sup&gt;a&lt;/sup&gt; (Z-score)</td>
<td>-0,12±1,08</td>
<td>0,09±0,94</td>
<td>0,448</td>
</tr>
<tr>
<td>HC&lt;sup&gt;b&lt;/sup&gt; (Z-score)</td>
<td>-0,29±1,05</td>
<td>0,24±0,91</td>
<td>0,052</td>
</tr>
<tr>
<td>TCD&lt;sup&gt;c&lt;/sup&gt; (Z-score)</td>
<td>-0,14±1,04</td>
<td>0,11±0,97</td>
<td>0,369</td>
</tr>
</tbody>
</table>

<sup>a</sup>Biparietal diameter. <sup>b</sup>Head circumference. <sup>c</sup>Transcerebellar diameter.

Note: Data are expressed as mean and standard deviation. P Value < 0.05 indicates significant difference.

Table 4: The relationship of some Doppler parameters between groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHD group (n= 30)</th>
<th>Control group (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-PI&lt;sup&gt;a&lt;/sup&gt; &lt; 5 percentile</td>
<td>2/30 [% 6,6]</td>
<td>1/30 [%3,3]</td>
<td>0,624</td>
</tr>
<tr>
<td>UA-PI&lt;sup&gt;b&lt;/sup&gt; &gt; 95 percentile</td>
<td>5/30 [%16]</td>
<td>2/30 [% 6,6]</td>
<td>0,227</td>
</tr>
<tr>
<td>CPR&lt;sup&gt;c&lt;/sup&gt; &lt; 1</td>
<td>3/30 [%10]</td>
<td>1/30 [%3,3]</td>
<td>0,334</td>
</tr>
</tbody>
</table>

<sup>a</sup>Middle cerebral artery pulsatility index. <sup>b</sup>Umbilical artery pulsatility index. <sup>c</sup>Cerebroplacental ratio.

Note: Data are expressed as number [%] where appropriate. P Value < 0.05 indicates significant difference.

Discussion

In this prospective case-control study, we demonstrated that umbilical artery RI and systole/diastole ratio (S/D) were higher in the CHD group than in the control group. There were no statistically significant differences between groups in MCA-PI and UA-PI. HC was statistically lower in the CHD group compared to the control group. Participants in the two groups had no significant differences, including MCA-PI < 5 percentile, UA-PI > 95 percentile, and CPR < 1.

It has been observed that fetuses diagnosed with congenital heart disease may have poor long-term neurodevelopmental outcomes, even in the absence of additional organs and genetic abnormalities. CHD has been associated with neurologic outcomes such as brain white matter damage, cortical developmental abnormalities, poor academic performance, decreased learning ability, and impaired motor skills in childhood. Although perioperative hypoxia and thromboembolic events are among the conditions that may lead to these adverse outcomes, recent studies have found that intrauterine effects may...
also contribute to brain damage unrelated to the surgical process.\textsuperscript{6,16}

Many hypotheses have been proposed to understand prenatal findings in CHD cases, but the mechanisms remain unclear. Studies have uncovered variations in placental development, the effects of genetic factors leading directly to disease onset on brain development, and cerebral hemodynamic changes that may be related to the proposed brain damage and outcomes.\textsuperscript{17-21} It has been suggested that vasodilation or sparing of the brain may occur in the cerebral circulatory system to provide adequate oxygen and nutrients to the brain because of decreased flow in the carotid arteries in forms of CHD forms that may cause reverse flow in the aortic arch.\textsuperscript{22} This reflects the fact that fetal brain surfaces respond well to hypoxia and that protective mechanisms are activated in the event of hypoxia in the first stage.

Several studies suggest that brain perfusion may vary depending on the form of CHD.\textsuperscript{22-24} Well-oxygenated placental blood is thought to be delivered to the brain via shunts in CHD types with anatomic variations that result in right-to-left shunts. In left-sided lesions, there are studies showing that well-oxygenated placental blood may be associated with brain lesions and developmental delays as a result of decreased cerebral blood flow.\textsuperscript{22-24} However, the finding of developmental delays in childhood in CHD forms with normal in utero perfusion confuses the issue of whether the CHD form is a predictor. Masoller et al. reported in their study of fetal Doppler brain findings that the anatomic form of CHD is not an independent predictor of abnormal fetal brain development.\textsuperscript{20}

In addition to Doppler parameters, studies have found a smaller HC in all types of CHD.\textsuperscript{2-6} A smaller HC ratio has been shown to be present in pathologies such as HLHS, TGA, and TOF, and a smaller HC has been related to neurodevelopmental outcome.\textsuperscript{20,24,25} When ultrasound Doppler data were examined, MCA-PI was found to decrease with increasing gestational age in cases with CHD. However, a review paper indicated that no clear relationship with CPR could be established because of difficulties in combining the data, although it was found that this relationship was generally associated with significant placental insufficiency.\textsuperscript{24,26,27}

In our study, we compared middle cerebral artery and umbilical artery values with those of healthy pregnant women to examine placental and cerebral perfusion, ie, cerebroplacental status, in CHD cases. We found high UA S/D and UA-RI values in CHD cases, although we did not detect a significant difference in UA-PI and MCA-PI values, which may be due to increased placental resistance. CPR < 1 is a cutoff value that has been suggested as an indicator of a brain-sparing effect. The contribution of right-to-left shunts and left-sided pathologies, as well as cases with normal Doppler flow, to heterogeneity in our groups may have resulted in the statistical difference not being found in the general cases. Low HC values were also found in our study in accordance with existing studies, but we found no significant difference in TCD, BPD, and inferior superior diameter of CSP. Our cases were those who were not diagnosed with fetal growth retardation or low gestational age without additional organs and genetic abnormalities. It is possible that the presence of additional pathology is an important parameter causing changes in biometric values.

There are some limitations of our study. First, our study did not perform subgroup analyzes according to the severity and anatomic variations of CHD forms. Second, the number of our study group included a small sample. Finally, our study did not use cortical malformations and other examinations that are not ultrasound examinations and can better assess brain volume.
Studies relying on additional methods such as magnetic resonance imaging, including subgroup analysis in larger series, could help to obtain more comprehensive results.

In conclusion, despite some limitations, our study has drawn attention to the changes in cerebroplacental flow and the level of decreased HC in CHD cases. It is not yet clear to what extent intrauterine and various forms of CHD contribute to future neurological changes. Metabolic and blood flow changes in the brain need to be supported by future studies with larger series, additional imaging techniques, and subgroup analyzes.

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