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Effect of Preeclampsia On Fetal Cardiac Output

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ABSTRACT

We hypothesized that there may be a change in fetal cardiac output due to the increase in placental vascular resistance in pregnancies with preeclampsia. We aimed to compare fetal cardiac output values in pregnancies with preeclampsia and healthy pregnancies.

This prospective case-control study involves 32 pregnant women with preeclampsia and 32 healthy women between the 32-34 gestational weeks. Right and left ventricular outflow systolic peak flow velocities (PSV) were measured and the velocity-time integral (VTI) was obtained by manually tracing the area under the PSV waveform. Stroke volume (SV) was obtained by multiplying the aortic and pulmonary valve cross-sectional area by the VTI. Cardiac output (CO) was found by multiplying the right and left SV with the fetal heart rate per minute (FHR). Right and left cardiac output values were compared between the study groups.

The left CO value was lower in the PE group, but this difference was not statistically significant. Right cardiac output was found to be significantly lower in the PE group ($p<.001$). Although umbilical artery and ductus venosus pulcatility index (PI) were higher and middle cerebral artery PI was lower in the preeclampsia group, these differences were not statistically significant.

The presented study shows that the right ventricular output significantly decreased due to abnormal placentation, increased placental vascular resistance and high afterload in pregnancies with preeclampsia.

Keywords: Cardiac Output, Pre-Eclampsia, Ultrasonography, Prenatal

Introduction

Preeclampsia (PE), which is characterized as maternal hypertension, proteinuria, and insufficient placental invasion, is critically important in terms of fetal/maternal morbidity and mortality (1-3). 10–15% of all pregnancies are complicated by hypertension, and preeclampsia affects 2–8% of pregnant women (3). PE's main disorders are insufficient trophoblastic invasion in the maternal spiral arteries, endothelial damage in the uteroplacental and systemic circulation, and vasospasm. Due to insufficient placentation, placental perfusion decreases and the subsequent hypoxic environment results in free radical formation, oxidative stress, endothelial activation and increased placental vascular resistance (4). The oxidative stress exposed in the intrauterine period in PE may cause changes in the functions and morphology of the fetal heart (5). In addition, high placental resistance in PE has important effects on fetal circulation (6). The most important of these is the increase in afterload, which is one of the factors affecting the contractility of the fetal heart and fetal cardiac output (CO) (7).

Fetal cardiac function is one of the best indicators of fetal well-being. The main factor determining the right ventricular afterload is the resistance in the placental circulation, and cerebrovascular resistance is the main determinant of left ventricular afterload (8). In pregnancies with PE, selective peripheral vascular resistance changes occur due to placental insufficiency and vasospasm and affect cardiac hemodynamic findings (4). These intracardiac hemodynamic changes shift cardiac output in favor of the left ventricle, preserving brain perfusion [9]. Studies have shown that preeclampsia can cause fetal cardiac dysfunction by myocardial injury, oxidative stress, and biochemical changes (10). Moreover, changes in cardiac functions were found in infants exposed to preeclampsia in the intrauterine period in long-term follow-ups after birth (11).

In the presented study, we hypothesized that there may be a change in fetal cardiac output due to the increase in placental vascular resistance in pregnancies with preeclampsia. We aimed to

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compare fetal cardiac output values in pregnancies with preeclampsia and healthy pregnancies.

Materials and Methods

Study Design: This prospective case-control study includes 64 pregnant women between 32–34 weeks of gestation who were admitted to the perinatology clinic between December 2022 and March 2023. Thirty-two pregnant women diagnosed with preeclampsia constituted the study group and 32 healthy pregnant women whose gestational weeks were matched with the case group constituted the control group.

Gestational weeks were calculated according to the last menstrual period and confirmed with crown-rump length (CRL) at 11–14 weeks of ultrasonography.

Pregnancies with maternal chronic disease (diabetes mellitus, chronic autoimmune inflammatory diseases, chronic hypertension, nephrotic syndrome, chronic kidney diseases, chronic liver, and hematological diseases), fetal growth retardation (FGR), preterm premature rupture of membranes (PPROM), fetal anomalies, chorioamnionitis and other maternal infections were excluded from the study. In addition, preeclampsia cases that could not wait for fetal cardiac evaluation and required emergency treatment were not included in the study.

The study was started after approval from the Ethics Committee and written informed consent was obtained from all participants (E2-22-3000).

Diagnosis of Preeclampsia: The diagnosis of preeclampsia was made according to the criteria of the American College of Obstetricians and Gynecologists (ACOG); new onset after 20 weeks of pregnancy, with systolic blood pressure (SBP) ≥ 140 or diastolic blood pressure (DBP) ≥ 90 in at least two measurements four hours apart, accompanied by one of the following: proteinuria (≥ 300 mg/24 hours or ≥ +2 dipsticks) thrombocytopenia (platelet count <100000/μL), pulmonary edema, renal insufficiency (creatinine >97μmol/L), new-onset headache, impaired liver function (more than twice normal concentration) or visual symptoms were considered preeclampsia (12).

Estimated Fecal Weight, Estimated Fetal Weight: All ultrasonographic examinations were performed by a single perinatology fellow (DUH) blind to the knowledge of which patients are in the case or control group, using the Voluson E8 ultrasound system (GE Medical System, Milwaukee, WI, USA). Fetal biometric measurements estimated fecal weight (EFW), amniotic fluid index and fetal well-being. Pregnancies with EFW below the 10th percentile for gestational age were not included. Umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV), uterine artery (UtA) and pulsatility indices (PI) were measured using spectral Doppler. The mean uterine artery (MUtA) PI was found by taking the average of the right and left uterine artery PI.

Fetal cardiac evaluation was performed using a Voluson E8, with a 2-5 MHz convex transducer. First, cardiac anomaly screening was performed and pregnancies with any cardiac anomaly were excluded. Aortic valve and pulmonary valve annulus were measured edge-to-edge in the long or short axis section of the ventricles when the valves were open in the mid-systole. Right and left ventricular outflow systolic peak flow velocities (PSV) were measured by keeping the insonation angle below 20 degrees and placing the pulsed Doppler sample volume distal to the valve annulus (13-15). The velocity-time integral (VTI) was obtained by manually tracing the area under the PSV waveform over a single cardiac cycle. Stroke volume (SV) was obtained by multiplying the aortic and pulmonary valve cross-sectional area by the VTI. Cardiac output (CO) was found by multiplying the right and left SV with the fetal heart rate per minute (FHR). All measurements were repeated twice and the averages were recorded.

Ultrasonographic cardiac measurements were made before any treatment because it has been reported that antihypertensive drugs used for neuroprotective purposes and MgSO4 treatment may affect fetal cardiac functions (16). Patients who were hemodynamically unstable and who received emergency treatment were excluded from the study.

Statistical Analysis: G Power software (version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany) was used to calculate the sample size. With a a power of 95% and p-value of 0.05, an effect size of 0.80 was determined for the sample size. There should be at least 31 cases. We planned to obtain one control for each case. Statistical analyzes were performed using SPSS (IBM SPSS Statistics 24). For quantitative data with normal distribution, descriptive statistics were given as mean ± standard deviation, and the "Independent t-test" was used to compare two independent groups. The distribution of the fetal right and left ventricular output measurements between the

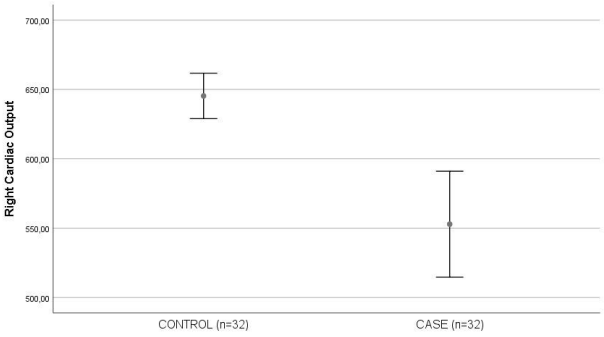

Fig.1. The distribution of The Fetal Right Ventricular Output Measurements Between The Study Groups

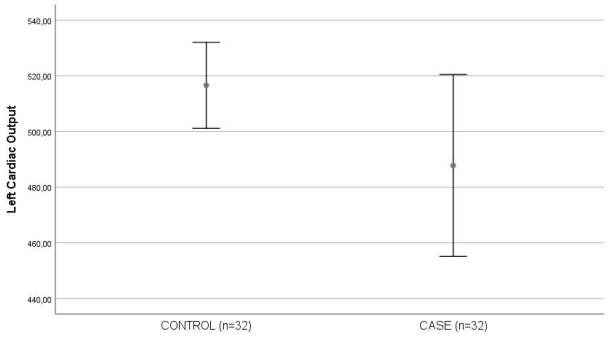

Fig. 2. The Distribution of The Fetal Left Ventricular Output Measurements Between The Study Groups

study groups was shown with the boxplot. Box describes the interquartile range, with the middle line across the box symbolizing the median.

Results

A total of 64 pregnant women were included in our study—32 of whom were diagnosed with preeclampsia and 32 healthy pregnancies. Table 1 shows the maternal characteristics and fetal ultrasonographic data of the study groups. The groups were similar in terms of maternal age, gravidity, parity, number of abortions, gestational week at which evaluation was made and pre-pregnancy body mass index (BMI). The mean SBP was 146 +/-6 and the mean DBP was 89 +/-4 in the PE group.

There was no significant difference between estimated fetal weights (EFW) and percentiles of EFW by gestational week. Although UA and DV PI was higher and MCA PI was lower in the preeclampsia group, these differences were not statistically significant. The mean uterine artery PI was detected to be significantly higher in the case group ($p<.001$).

Right and left cardiac output was obtained by multiplying the pulmonary and aortic valve area, VTI and fetal heart rate per minute. The right and left cardiac output results were compared between the groups. The distribution of the right and left cardiac output values between the groups is shown in Figures 1 and 2. The left CO value was lower in the PE group, but this difference was not statistically significant. Right cardiac output was found to be significantly lower in the PE group ($p<.001$).

The perinatal outcomes of both groups were shown in Table 2. The differences between the study groups in terms of Apgar score at 1st and 5th minutes, and umbilical cord pH values were not significant whereas gestational week at birth and accordingly birth weight were found to be significantly lower in the PE group ($p<.001$).

Discussion

In the present study, the effect of preeclampsia on fetal cardiac output was investigated. We found that cardiac output in the PE group, especially in the right ventricle, significantly decreased compared to the control group. Uterine artery Doppler pulsatility index values, which we examined to evaluate the perfusion of the fetomaternal unit, were found to be significantly higher in the PE group. Mean gestational age at birth, and therefore birth weight, was found to be significantly lower in the PE group.

In preeclampsia pregnancies, significant effects on fetal circulation occur due to abnormal placentation and associated increased placental vascular resistance. In normal healthy pregnancies, the resistance and pressure of the blood flow in the fetomaternal bed are low, but the flow rate is high. However, in preeclampsia, there is a high resistance and low flow circulation because of insufficient trophoblastic invasion of the spiral arteries. This high resistance in placental flow may affect fetal cardiac output by increasing the right ventricular afterload. An increase in afterload may affect myocardial contractility and cause a decrease in preload. It is observed that the right ventricular output decreases due to abnormal placentation and deterioration of perfusion, while redistribution of the fetal circulation causes a decrease in left ventricular afterload, thus shifting cardiac output to the left ventricle.

The present study demonstrated a decrease in both ventricular outputs, with a more significant reduction in right ventricular output in the PE group. We found umbilical artery PI was slightly higher and MCA PI was slightly lower, but these changes were not statistically significant in PE group. With these findings in our study, we can

Table 1. Maternal Characteristics and Fetal Ultrasonographic Data of Study Groups

	Case (n=32)	Control (n=32)	p value
Age (years)	27.8+/-5.9	29 +/-4.3	.375*
Gravidity	2+/-1	2+/-1	.931*
Parity	1+/-0	1+/-0	.566*
GA (weeks)	33+/-1	33+/-1	.632*
BMI (kg/m2)	28.9+/-5.2	27.6+/-3.4	.081*
EFW (gram)	1876+/-600	1939+/-557	.167*
EFW (percentile)	44+/-17	51+/-13	.432*
UA PI	1.03 +/-0.3	1+/-0.1	.378*
MCA PI	1.63+/-0.3	1.67+/-0.6	.713*
DV PI	0.72+/-0.2	0.63+/-0.3	.053*
MUtA PI	1.1+/-0.5	0.8+/-0.2	<.001*
RCO (ml/min)	553+/-105	645+/-45	<.001*
LCO (ml/min)	488+/-90	517+/-43	.109*

Values are presented with mean +/-standart deviation.
*Independent t test
Abbreviations: GA, gestational age; BMI, body mass index; EFW, estimated fetal weight; UA, umbilical artery; PI, pulcatility index; MCA, middle cerebral artery; DV, ductus venosus; MUtA, mean uterine artery; RCO, right cardiac output; LCO, left cardiac output

Table 2. Perinatal Outcomes of The Study Groups

	Case (n=32)	Control (n=32)	p value
GA at birth (weeks)	35+/-2	38+/-1	<.001*
Birth weight (gram)	2400+/-332	3335+/-260	<.001*
APGAR score at 1 minute	7+/-1	7+/-1	.872*
APGAR score at 5 minutes	8+/-1	9+/-1	.296*
Umbilical artery pH	7.32+/-0.1	7.37+/-0.1	.068*

Values are presented with mean +/-standart deviation.
*Independent t test
Abbreviations: GA, gestational age

suggest that uterine artery PI increased, and right ventricular CO decreased due to the increase in placental vascular resistance and right ventricular afterload, but there was no significant fetal circulation redistribution since there was no increase in left ventricular output and no significant decrease in MCA PI. These findings may suggest that decreased right ventricular CO may precede redistribution of fetal circulation. In previous studies, it has been reported that cardiac output in fetuses with FGR and in fetuses with PE accompanied by FGR shows distribution in favor of the left ventricle (17,18).

The fetal heart is the main organ that provides the adaptation of the fetus to the intrauterine environment, and fetal heart functions may be affected according to the changing microenvironment (19). Fetal cardiac output was found to increase in both ventricles with gestational week, but the right cardiac output was higher than the left ventricular output during pregnancy (20). Obstetric and maternal reasons that may impair placental perfusion such as FGR, PE, maternal chronic inflammatory diseases and intrauterine infections may influence fetal CO (13-15,17). In the study examining cardiac morphology and functions in fetuses with early and late onset FGR, it was observed that right and left cardiac outputs were significantly decreased in both groups compared to the control group (17). Fetal cardiac functions were evaluated in mild preeclampsia cases and a decrease in cardiac output and MCA PI were found in mild preeclampsia cases (21). In the early and late preeclampsia groups, cardiac output measurements were evaluated according to whether they were with or without FGR, and while high cardiac output was observed in early and late PE cases without FGR, low cardiac

output was found in PE cases with FGR [22]. Contrary to this study, we found decreased fetal left and right cardiac outputs in PE pregnancies, and we evaluated isolated PE cases by excluding fetuses with FGR.

The strengths of our study are that it is a case-control study with a prospective design, and it includes isolated preeclampsia cases that exclude FGR. In many studies evaluating fetal cardiac output in pregnant women with preeclampsia, the association of FGR makes it difficult to determine the effect of isolated preeclampsia on fetal cardiac output.

Study Limitations: The relatively small number of patients and lack of confirmation with postnatal follow-ups are the limitations of our study. Comparative studies in early/late preeclampsia and mild/severe preeclampsia subgroups with increased number of patients and postnatal follow-ups may provide more benefits.

The presented study shows that the right ventricular output significantly decreased due to abnormal placentation, increased placental vascular resistance and high afterload in pregnancies with preeclampsia. The decrease in the right cardiac output before a significant change in MCA and UA dopplers may be useful as an early fetal Doppler finding in the clinical management of preeclampsia pregnancies.

Conflict of Interests: The authors declare that there is no conflict of interests.

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