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Research paper

Does betamethasone therapy impact fetal multivessel Doppler parameters?

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Abstract

Introduction: The objective of this study was to test the hypothesis that antenatal corticosteroid therapy alters fetal cardiopulmonary and uteroplacental blood flow in pregnancies.

Material and methods: Twenty-seven singleton pregnancies between 28 and 34 gestational weeks classified as at risk of preterm birth were included prospectively. We evaluated fetal main pulmonary artery (MPA), left and right pulmonary artery (PA), left myocardial performance index (Tei index), tricuspid valve (TV), umbilical artery (UmA), middle cerebral artery (MCA), and ductus venosus (DV) parameters before and 48 hours and 7 days after antenatal steroid administration.

Results: The mean age was 31 years, and the mean gestational age was 31 weeks. The UmA S/D (Systole/Diastole) ratio, PI (pulsatility index) and RI (resistive index) values, and Doppler parameters of other vessels were not different when comparing between before and after steroid administration. Except for MCA PSV (peak systolic velocity) values, the other MCA Doppler parameters (S/D, PI, RI) were all significantly decreased. The cerebroplacental ratio (CPR) and CPR percentile values decreased significantly. All tested cardiac parameters were unchanged, except MPA ejection time (ET) ($p = 0.016$).

Conclusions: Our data demonstrate altered fetal MCA and CPR with corticosteroid therapy. These data suggest that antenatal corticosteroid therapy has no impact on any Doppler parameters of fetal cardiopulmonary and uteroplacental blood flow in pregnancies.

Key words: betamethasone, lung maturity, Doppler, antenatal corticosteroid.

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Introduction

Maternal treatment with an antenatal corticosteroid (ACS) is the standard of care worldwide for fetuses at risk of adverse outcomes from preterm birth [1]. In the 1970s, Liggins and Howie first demonstrated that ACSs decrease the risk of respiratory distress syndrome (RDS) and neonatal death [1]. ACSs are routinely administered at between 24 and 34 weeks of gestation in pregnancies at high risk of preterm delivery [2]. The optimal timing of ACS administration is 1-7 days before preterm birth [3]. Preterm birth is the leading cause of neonatal mortality and the most common reason for antenatal hospitalization. Approximately 12% of all live births occur preterm.

Preterm birth accounts for about 70% of neonatal deaths and 36% of infant deaths, as well as for 25-50% of cases of long-term neurologic impairment in children [4].

Doppler examination is an essential tool to assess fetal well-being. Conflicting results have been reported regarding the effect of exogenous corticosteroids on fetal hemodynamics. Deren et al. and Rotmensch et al. have demonstrated that betamethasone administration can cause significant but transient suppression of fetal breathing and body movements, although the middle cerebral artery (MCA) and umbilical artery (UmA) Doppler indices were found to be unaffected [5, 6]. Cohlen et al. found no significant change in the pulsatility index of any of the fetal vessels [7]. Chitrit et al. found a transient effect in fetal MCA impedance [8].

A corticosteroid administered antenatally might increase the production of surfactant in the fetal lungs. Therefore, corticosteroid administration might cause a reduction in pulmonary vascular resistance and an increase in pulmonary blood flow [9]. Here we aimed to test this theory via multi-vessel Doppler parameters before and after steroid administration.

Material and methods

This was a prospective cohort study. During March 2018 – March 2019, 27 singleton pregnancies between 28 and 34 gestational weeks with a diagnosis threat of preterm birth were included prospectively. To be eligible, patients had to have received betamethasone and a loading dose of nifedipine for tocolysis, followed by hydration and maintenance nifedipine therapy for 48 hours. Betamethasone (Celestone Cronodose, Schering-Plough, İstanbul, Turkey) was administered as 2 doses of 12 mg each, administered 24 hours apart. Fetuses with intrauterine growth restriction (IUGR), oligohydramnios, polyhydramnios, or fetal anomaly were excluded from the study. Other maternal indications for exclusion were preeclampsia, eclampsia, HELLP syndrome, premature preterm rupture of membranes, placenta previa, or any chronic maternal disease. Patients with diabetes mellitus (gestational or pregestational) were not included in the study. We prospectively evaluated the fetal main pulmonary artery (MPA), left and right pulmonary artery (PA), left myocardial performance index (MPI, Tei index), tricuspid valve (TV), umbilical artery (UmA), middle cerebral artery (MCA), and ductus venosus (DV) parameters before and at 48 hours and 7 days after steroid administration. The Doppler indices of interest included peak systolic velocity (PSV), resistive index (RI), pulsatility index (PI), systolic/diastolic ratio (S/D ratio), acceleration time/ejection time ratio (AT/ET ratio) – MPA, E/A ratio – TV, left ventricle Tei index parameters (isovolumetric contraction time [ICT], isovolumetric relaxation time [IRT], ejection time [ET]), and DV A wave.

The angle of insonation was maintained at less than 30°, and the sample volume was set at 2 mm. The examinations were performed in the absence of fetal movements or breathing. Doppler study for the umbilical artery was obtained in a free loop, and for MCA it was obtained in a cranial transverse plan and 1 cm after its origin from the circle of Willis (Figure 1). The DV was identified at the transverse or sagittal plane before

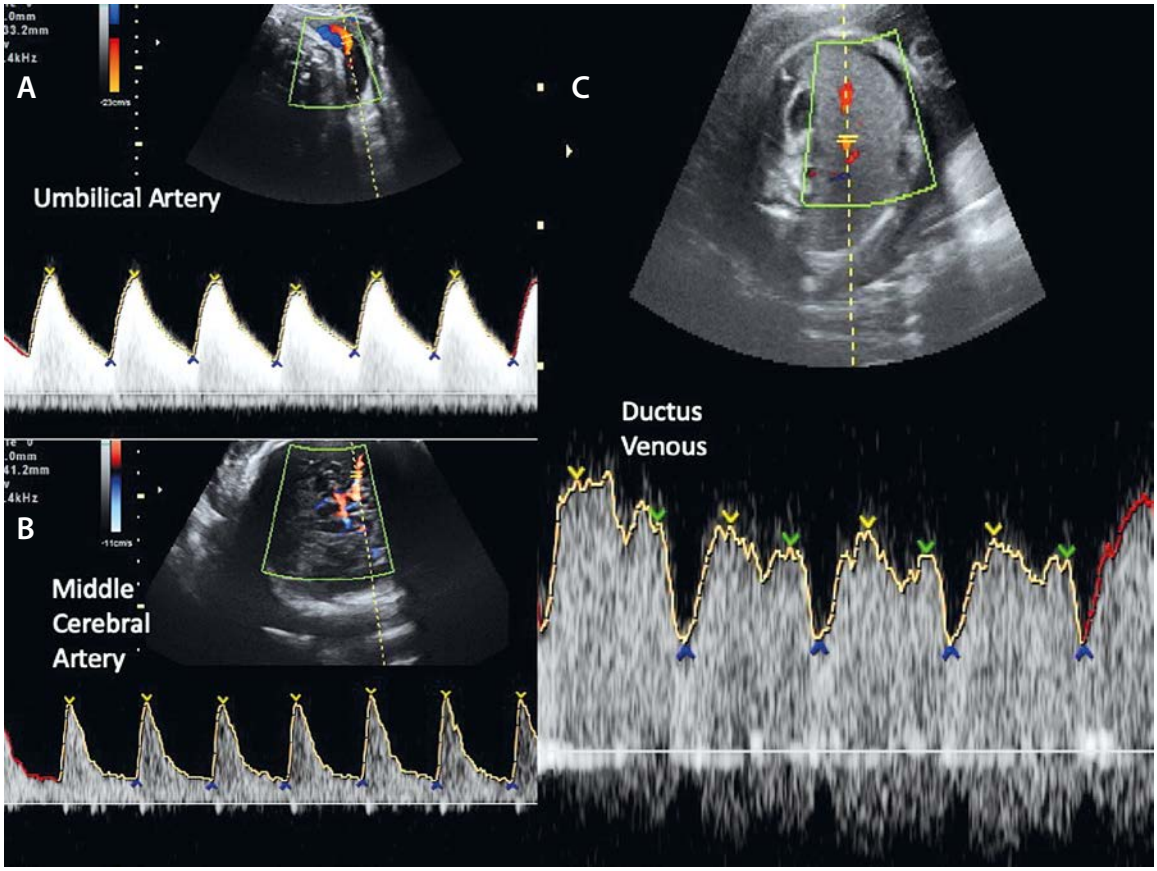

Figure 1. Fetal (**A**) umbilical Doppler, (**B**) middle cerebral artery, and (**C**) ductus venosus

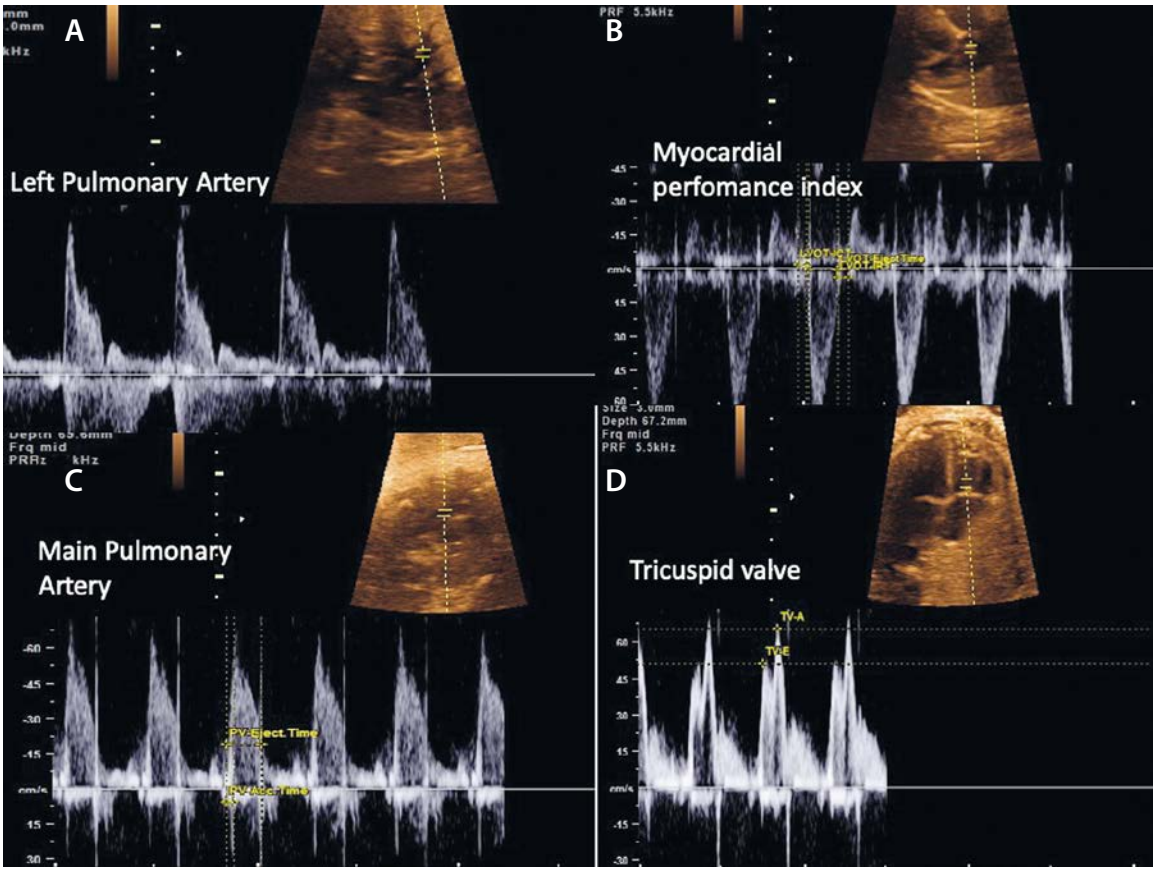

Figure 2. Cardiac Doppler (**A**) left pulmonary artery branch, (**B**) myocardial performance index with ICT, IRT, and ET, (**C**) main pulmonary artery with AT and ET, and (**D**) tricuspid valve with E-wave and A-wave

drainage to the inferior vena cava (Figure 1). The CPR was calculated by dividing the MCA PI by the UmA PI. CPR percentile values were obtained from a web-based calculator (https://medicinafetalbarcelona.org/calc).

Cardiac parameters (Figure 2) were obtained by conventional pulsed Doppler, keeping the insonation angle of the ultrasound beam as close to 0° as possible with respect to the direction of blood flow. Tricuspid E/A ratios were obtained by measuring the peak early (E) and late (A) transvalvular filling velocities obtained from a basal or apical 4-chamber view, placing the sample volume just below the valve leaflets. The left MPI was measured at the level of the left ventricular outflow tract view, illustrating the 4 chambers of the heart and the aorta arising from the left ventricle. The sample volume was placed to include both the ascending aorta and the mitral valve, where the clicks corresponding to the opening and closing of the 2 valves could be clearly visualized. In spectral Dopplers, ICT, IRT, and ET were calculated using the beginning of mitral and aortic opening and closing clicks, and the MPI was calculated as (ICT+IRT)/ET. At the axial view of the thorax, the MPA was studied until midway between the pulmonary valve and the bifurcation of the right and left branches. The pulsed Doppler sample gate was adjusted to 2-3 mm, and the angle of insonation was maintained as close to 0° as possible. To obtain the AT/ET, the time interval from the beginning of the ventricular systole to the achievement of peak velocity (AT) was divided by the time interval from the beginning to the end of the ventricular systole (ET). When a clear sonographic transverse cross-section of the fetal chest was obtained at the level of the cardiac 4-chamber view, the color Doppler mode was switched on to visualize the pulmonary circulation. Both right and left main PAs were examined. Waveforms were obtained from the middle segment of the PA. The sample volume was adjusted to 2 mm, and the insonation angle was kept below 30°. At least 3 uniform waveforms from each artery were obtained for measurement (Figure 2).

The pre-steroid-administration Doppler parameters were used as the control condition, and the changes after steroid administration were calculated. All patients' sonographic examinations were made by one expert physician (HO), and only one sonographic machine was used for this (E10, GE Healthcare, Milwaukee, Wisconsin USA).

Statistical analysis

Data were analyzed with IBM SPSS v23. Conformity to normal distribution was examined using the Shapiro-Wilk test. Repeated analysis of variance test for normally distributed variables and Friedman test for non-normally distributed variables were used to examine the changes of parameters within the group over time. Analysis results were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data and as frequency (percentage) for categorical data. The significance level was taken as $p < 0.05$.

Ethical approval

The Gazi University Ethics Board (No:374, 14/05/2018) and Turkey Pharmaceuticals and Medical Devices Agency Clinical Research Department (17-AKD-155) approved this study, and written informed consent was received from each participant. A copy of the patient declaration of consent is available upon request.

Results

The mean age of the participants was 31 years, and the mean gestational age was 31 weeks. UmA S/D ratio, PI, RI values, and none of the Doppler parameters at 48 hours and 7 days after steroid administration changed statistically according to the Doppler parameters from before steroid administration.

There was no significant change in MCA PSV values, but there was a statistically significant decrease in S/D, PI, and RI values ($p = 0.001$, $p = 0.001$, and $p \leq 0.001$, respectively). Also, there was a statistically significant decrease in CPR ($p = 0.028$). When we analyzed the percentile values according to the weeks of gestation, this decrease remained significant ($p = 0.025$). The change in the DV PI value was not statistically significant, but the A wave value was statistically higher after steroid administration ($p = 0.049$) (Table 1).

When we evaluated the cardiac Doppler parameters, there was no statistically significant change in the parameters related to the right heart with TV E wave, TV A wave, TV E/A ratio, MPA AT, MPA AT/ET ratio, and right and left PA PI values. Only a statistically significant reduction in the time of the MPA ET was observed ($p = 0.016$) (Table 2). In the MPI, which is one of the cardiac systolic function parameters, no statistically significant changes were found in the ICT, IRT, ET, Tei index, or percentile values (Table 2).

Discussion

In this study we hypothesized that if corticosteroid administered antenatally increases the production of surfactant in the fetal lungs, we could evaluate this effect by fetal Doppler, especially pulmonary artery Doppler. Pulmonary vessel (MPA, left and right PA Doppler), cardiac parameters (TV, Tei index), and other Doppler data show no change following steroid administration. A statistically significant difference was seen only at MPA ET ($p = 0.016$). Our data also demonstrate altered fetal MCA and DV blood flow with corticosteroid therapy. These data suggest that antenatal corticosteroid therapy does not impact any Doppler parameters of fetal cardiopulmonary and uteroplacental blood flow in pregnancies.

Table 1. Fetal systemic vessel Doppler parameters before and after betamethasone administration ($n = 27$)

Doppler parameters		Just before steroid administration	At 48th hour	At 7th day	*P*-value
Umbilical artery PI	mean ± SD	1 ±0.1	0.9 ±0.1	0.9 ±0.1	0.367
	median (min.-max.)	0.9 (0.6-1.3)	0.9 (0.7-1.2)	0.9 (1-1)	
Umbilical artery S/D	mean ± SD	2.8 ±0.5	2.7 ±0.4	2.5 ±0.3	0.297
	median (min.-max.)	2.7 (1.9-4)	2.5 (2.1-3.3)	2.5 (2-3)	
Umbilical artery RI	mean ± SD	0.6 ±0.1	0.6 ±0.1	0.6 ±0	0.367
	median (min.-max.)	0.6 (0.5-0.8)	0.6 (0.5-0.7)	0.6 (1-1)	
MCA PSV	mean ± SD	44.2 ±9	40.9 ±8.1	43.8 ±6.7	0.101
	median (min.-max.)	43 (28-59.7)	40.6 (24.8-55.8)	44.7 (32-54)	
MCA S/D	mean ± SD	6.7 ±2.3	5.8 ±2.2	6.1 ±7.5	0.001
	median (min.-max.)	6.6 (4-12.8)	5.3 (2.5-10.6)	4.1 (3-37)	
MCA RI	mean ± SD	0.86 ±0.05	0.80 ±0.05	0.77 ±0.7	< 0.001
	median (min.-max.)	0.9 (0.8-0.9)	0.8 (0.6-0.9)	0.8 (1-1)	
MCA PI	mean ± SD	1.9 ±0.3	1.8 ±0.4	1.6 ±0.4	0.001
	median (min.-max.)	1.9 (1.5-2.7)	1.8 (0.9-2.5)	1.5 (1-3)	
CPR	mean ± SD	2.2 ±0.5	2.0 ±0.4	1.8 ±0.4	0.028
	median (min.-max.)	2 (1.4-2.8)	1.9 (1.4-3.1)	1.8 (1-2)	
CPR percentile	mean ± SD	44.6 ±30.1	40.8 ±27.3	29.4 ±22	0.025
	median (min.-max.)	40 (7-92)	33 (6.97)	21 (2-73)	
DV PI	mean ± SD	0.6 ±0.2	0.5 ±0.2	0.5 ±0.1	0.051
	median (min.-max.)	0.6 (0.3-1.1)	0.5 (0.2-0.9)	0.5 (0-1)	
DV A wave	mean ± SD	19.2 ±.8.4	24.04 ±9	24.0 ±8.8	0.049
	Median (min.–max)	18.5 (7.5-42.2)	24 (7-40)	23 (12-46)	

PI – pulsatility index, RI – resistive index, S/D – systolic/diastolic, PSV – peak systolic velocity, CPR – cerebroplacental ratio, MCA – middle cerebral artery, DV – ductus venosus; p < 0.05 was significant.

Table 2. Fetal cardiac Doppler parameters before and after betamethasone administration ($n = 27$)

Doppler parameters		Just before steroid administration	At 48th hour	At 7th day	*P*-value
Tricuspid E wave	mean ± SD	345 ±87.3	349.6 ±59	381.6 ±79.3	0.331
	median (min.-max.)	357 (77-509)	331 (259-464)	368 (248-570)	
Tricuspid A wave	mean ± SD	489.4 ±115.4	494.9 ±84.1	560.7 ±122.9	0.143
	median (min.-max.)	521 (103-666)	471 (347-968)	537 (354-928)	
Tricuspid E/A ratio	mean ± SD	0.7 ±0.1	0.7 ±0.1	0.7 ±0.1	0.599
	median (min.-max.)	0.7 (0.6-0.9)	0.7 (0.6-0.8)	0.7 (1-1)	
MPI-ICT	mean ± SD	42.8 ±10.2	41.4 ±12	45.4 ±12.3	0.319
	median (min.-max.)	40 (26-66.7)	40 (22.2-66.7)	44.4 (26-80)	
MPI-ET	mean ± SD	161.8 ±15.5	149.4 ±20.9	159 ±14.1	0.396
	median (min.-max.)	164 (129-191)	151 (71.1-178)	160 (138-178)	
MPI-IRT	mean ± SD	51.6 ±8.9	54.1 ±18.7	52.2 ±10.7	0.438
	median (min.-max.)	53.3 (35-66)	53 (35-124)	53 (22-76)	
MPI (Tei index)	mean ± SD	0.6 ±0.1	0.6 ±0.2	0.6 ±0.1	0.214
	median (min.-max.)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.6 (0-1)	
MPI percentile	mean ± SD	89.6 ±18.8	91.5 ±15.6	92.3 ±19.2	0.361
	median (min.-max.)	98 (28-99)	99 (30-99)	98 (15-99)	
MPA AT	mean ± SD	49.1 ±6.8	45.7 ±6.4	45.7 ±7.5	0.057
	median (min.-max.)	49 (36-37)	44 (36-32)	44 (36-62)	
MPA ET	mean ± SD	197.8 ±22.2	193.3 ±19.1	181.2 ±28.6	0.016
	median (min.-max.)	196 (160-271)	187 (160-249)	178 (100-249)	
MPA AT/ET	mean ± SD	0.2 ±0	0.2 ±0	0.2 ±0	0.345
	median (min.-max.)	0.3 (0.2-0.3)	0.2 (0.1-0.3)	0.2 (0-0)	
Right PA PI	mean ± SD	3.1 ±0.6	3.3 ±0.6	2.9 ±0.5	0.368
	median (min.-max.)	3.1 (2.3-4.2)	3.2 (2.3-4.9)	2.9 (2-4)	
Left PA PI	mean ± SD	2.9 ±0.5	3 ±0.7	2.7 ±0.5	0.141
	median (min.-max.)	2.9 (2-3.8)	2.9 (2-5.9)	2.5 (2-4)	

PI – pulsatility index, ICT – isovolumetric contraction time, ET – ejection time, IRT – isovolumetric relaxation time, MPI – myocardial performance index, MPA – main pulmonary artery, AT – acceleration time, ET – ejection time, PA – pulmonary artery (branch); $p < 0.05$ was significant.

Lindsley et al. compared a study group to an uncomplicated cohort without steroid therapy and found that fetuses treated with corticosteroids demonstrated significantly decreased MPA AT (median: 28.89 (22.22-51.11) vs. 33.33 (22.20-57.00), $p = 0.006$), while all other indices remained similar. Also, these authors detected no difference in pulmonary blood flow between fetuses that developed respiratory distress syndrome (RDS) and those that did not (31.56 ±6.842 vs. 32.36 ±7.265, $p = 0.76$) [10]. In our study, we did not detect any significant change at MPA AT, but MPA ET was lower at 48 hours (193.3 ±19.1) and 7 days (181.2 ±28.6) after steroid administration, than the measurement taken before (197.8 ±22.2) ($p = 0.016$). In our study, there was a trend to decrease at AT, but this change was not significant ($p = 0.057$). This corticosteroid-induced change might cause a reduction in pulmonary vascular resistance. Another cardiac parameter was the myocardial performance index (MPI), which reflects combined systolic and diastolic performance [11]. Vadivelu et al. reported that MPI was lower after steroid administration in an FGR group. However, Marchi et al. did not detect MPI changes in their FGR group, but the right ventricle MPI was higher than before steroid administration. Similarly to our study, Marchi et al. reported no significant change in MPI values between groups. Consistent with the literature [11, 12], in our study we detected no change in TV Doppler parameter values. Güngör et al. reported that there was no change in pulmonary artery branch indices [9]. Üstünyurt et al. detected a transient decrease in pulmonary branch artery indices at 24 and 48 hours [13]. In our study, we detected no significant change in pulmonary artery branch Doppler indices.

In the literature, there are conflicting data for systemic vessel Doppler changes after steroid administration. Some of these studies detected a transient Doppler effect at 24-48 hours, which was reversed at 4-7 days [9, 12, 14]. Thuring et al.

detected changes in the umbilical artery waveform in 12 of 15 cases ($p < 0.01$): from reversed to absent and from absent to positive diastolic flow [14]. Another study reported that umbilical artery PI was decreased in fetuses that develop RDS in the neonatal period [9]. İnan et al. detected no significant change at umbilical PI, but there was a significant change at RI [15]. In our study, we detected no significant differences in the umbilical artery Doppler indices before and after steroid administration.

Several studies have reported the effect of betamethasone on Doppler parameters of the MCA, and they found decreased or unchanged MCA PI levels in various patient groups [5, 6, 11, 12, 15]. In our study, except for MCA S/D, all other MCA Doppler indices had a significant change. In contrast, İnan et al. found a significant difference in S/D indices, but other parameters were not significant. Also, CPR and CPR percentile values changed significantly in our study. Similarly, Wijnberger et al. found a significant increase in the UA-PI/MCA-PI ratio in IUGR populations. The findings indicate that betamethasone decreases the vascular resistance index of MCA. Because of the CPR and CPR percentile changes, this effect was induced by betamethasone administration rather than gestational age change. The observed changes in the MCA doppler indices could be related to increased cerebral blood flow. Therefore, betamethasone could influence brain circulation. Concordant with the literature, DV PI remained unchanged in the present study [11, 12, 14, 15].

The strength of the present study was that our study population was a homogenous group and included only singleton pregnancies between 28 and 34 gestational weeks diagnosed as at risk of preterm birth. Moreover, unlike most studies, this study evaluated all commonly used all fetal circulation Doppler and and cardiac Doppler parameters for up to 7 days. The small sample size is a limitation of this study. Another important limitation of the study is that other cardiac parameters that may be significant were not used, and the number of patients that would allow subgroup analysis was not reached.

Conclusions

In conclusion, fetal multivessel Doppler velocimetry can reliably be obtained throughout gestation. Pulmonary vessel (MPA, left and right PA Doppler), cardiac parameters (TV, Tei index), and Doppler data revealed no changes due to steroid administration. Our data demonstrate altered fetal MCA and CPR with corticosteroid therapy. These data suggest that antenatal corticosteroid therapy does not impact any Doppler parameters of fetal cardiopulmonary and uteroplacental blood flow in pregnancies.

Conflict of interest

The authors declare no conflict of interest.

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