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Alterations in transcranial Doppler indices of pregnant women with complicated preeclampsia

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ABSTRACT

Objectives: We aimed to investigate alterations in transcranial Doppler indices (TCD) of the cerebral arteries between normotensive and preeclampsia (PE) pregnancies according to the presence of cerebral symptoms.
Study design: This cross-sectional study included 48 PE and 20 normotensive pregnancies, respectively. Doppler indices of the anterior, middle, and posterior cerebral arteries (ACA, MCA, and PCA, respectively) were compared between the PE and normotensive group.
Main outcome measures: Mean cerebral velocity (MCV), pulsatility index (PI), and resistance index (RI) were calculated using cerebral velocities. The cerebral perfusion pressure (CPP), resistance area product (RAP), and cerebral flow index (CFI) were computed using velocity and blood pressure. The PE group was subdivided according to the presence of cerebral symptoms and the TCD indices were compared between these groups.
Results: MCV and CFI of the PCA as well as CPP and RAP of all arteries were significantly higher, while PI and RI were significantly lower in PE group ($P < 0.05$). PI of the MCA had the highest sensitivity (91.7%), while PI of the PCA and RAP of the MCA had the highest specificity (95.0% each) for predicting PE-related cerebral complications. The positive likelihood ratio was highest in PI of the PCA (14.58). Among these parameters, CPP and RAP of the PCA were higher in PE patients showing cerebral symptoms than in those without symptoms.
Conclusions: These results suggest that pregnant women with PE had altered TCD indices and that prominent changes, thereof, especially in the PCA, contribute to the development of cerebral symptoms.

1. Introduction

Preeclampsia (PE) is a multisystem pregnancy-specific hypertensive disease that affects 2–8% of pregnancies and is the second leading cause of maternal morbidity and mortality worldwide. PE is associated with maternal complications such as cardiomyopathy, placental abruption, chronic hypertension, and cardiovascular disease. Among them, cerebral complications such as cerebral edema, hemorrhage, and eclamptic convulsion contribute to the primary cause of maternal mortality [1,2]. Because of these severe complications, research has been conducted on the pathogenesis of cerebral complications in PE, with new theories developing [3–5]. The failure of cytotrophoblasts invasion causes a lack of transformation in the spiral arteries, resulting in lower placental perfusion and ischemia. These phenomena lead to systemic endothelial dysfunction by the release of placental substances such as syncytiotrophoblast debris, antiangiogenic factors and oxidized lipids, and soluble endoglin [6,7]. Increased pressor responses, such as vascular reactivity and angiotensin II sensitivity in PE have been postulated as important etiologic factors in the development of PE [8,9]. Besides, responsiveness of angiotensin II is considered critical factors in the pathogenesis of hypertension and induced oxidative stress in cerebral arteries.[10,11]. Endothelial dysfunction and hypertension have been thought to play an important role in the development of cerebral complications by affecting the hemodynamics and autoregulation of cerebral vessels.[2].

Cerebral autoregulation is important to maintain adequate cerebral perfusion in response to changes in blood pressure (BP). However, as PE progresses, vascular damage occurs by endothelial dysfunction and hypertension, and these serial mechanisms provoke auto-regulation impairments. As a result, a cerebral overperfusion state progresses to cerebral complications such as cerebral edema, headache, visual disturbance, and seizure. In a previous study on TCD of PE patients,

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Riskin-Mashiah et al. demonstrated that a low pulsatility index (PI) and resistance index (RI) of the middle cerebral artery (MCA) were related to compensatory cerebral vasodilatation in PE pregnancies prior to cerebral symptom onset [12]. Belfort et al. reported that severe PE pregnancies had higher cerebral perfusion pressure (CPP) than mild PE pregnancies because of cerebral overperfusion [12–15].

Therefore, here we evaluated the hemodynamic changes in the main branches of the circle of Willis between normal and preeclamptic pregnant women using transcranial Doppler (TCD) and investigated which branches were mostly affected and which indices changed. Furthermore, we aimed to clarify the relationship between cerebral symptoms and these changes, and determine the predictive value of TCD parameters.

2. Materials and methods

The research was approved by the Institutional Review Board of Pusan National University Hospital in Busan, South Korea and all participants were signed a consent form to this protocol (No. H-1808-009-069). This cross-sectional study included 81 women with singleton pregnancies who visited our obstetrical clinic between March 2011 and April 2018. Before the TCD test, 13 PE pregnancies were excluded from the study because of conditions such as diabetes mellitus (DM) or gestational DM (n = 5), chronic hypertension (n = 5), eclamptic seizure (n = 1), and other connective disorders (n = 2). TCD was performed in pregnant women diagnosed with PE (n = 48) and healthy pregnant women (n = 20) (Fig. 1).

PE is defined as hypertension (BP ≥ 140/90) with proteinuria (≥0.3 g/24 h or 1+ dipstick) after 20 weeks' gestation. If the proteinuria is not present, it is diagnosed if patients have hypertension with thrombocytopenia (platelet count < 100,000/mL), elevated liver enzymes, renal insufficiency (serum creatinine > 97.26 μmol/L), pulmonary edema, and new-onset cerebral or visual disturbances [16]. Among the 48 patients with PE, 19 with a BP > 160/100 mmHg at admission were administered antihypertensive agents (hydralazine, calcium channel blocking agents) a priori and TCD was performed after BP stabilization.

All patients were examined in the supine position by two neurologists with at least 5 years of clinical experience. Our study used the power m-mode TCD, 2 channel-digital Doppler platform (PMD 150, Spencer Technologies, Seattle, WA, USA) with low -frequency pulsed transducers (2 MHz) to improve bone penetration. TCD indices were measured five times repeatedly at the trans-temporal window with the highest permeability and thinnest bone thickness on the left and right side of each patient's head. The averaged value was analyzed from both sides of the head. The cerebral arteries were insonated as follows: A1 segment of anterior communicating artery of ACA, M1 segment of MCA and P1 segment of posterior communicating artery of PCA. The velocity waveform was obtained at the depth which had the most stable hemodynamic waveform of each artery (ACA, 65–80 mm; MCA, 40–65 mm; and PCA, 55–70 mm) [17]

We measured BP at the brachial artery of both arms at the time of the TCD test and calculated mean arterial pressure and TCD indices using the following formula:

$$MAP = (BP_{systolic} + (2 \times BP_{diastolic}))/3.$$

Measured TCD values were calculated as follows:

$$PI = (Velocity_{systolic} - Velocity_{diastolic})/Velocity_{mean};$$

$$RI = (Velocity_{systolic} - Velocity_{diastolic})/Velocity_{systolic};$$

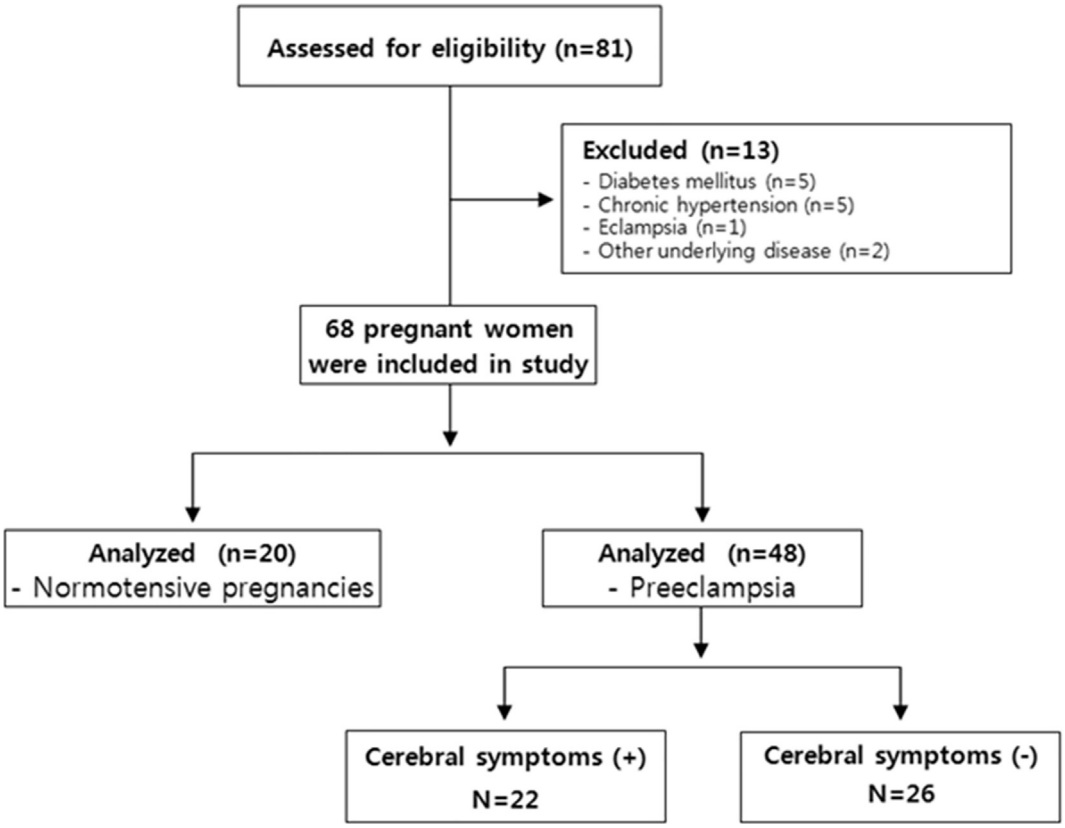

Fig. 1. Flowchart of the study population. Flowchart showing the study population, analysis between women with normotensive and preeclamptic pregnancies and comparative analysis according to the cerebral symptom status.

Cerebral perfusion pressure (CPP)=(Velocity$_{mean}$ /(Velocity$_{mean}$ − Velocity$_{diastolic}$) × (Mean arterial pressure−BP$_{diastolic}$);

Resistance area product (RAP) = Mean arterial pressure/Velocity$_{mean}$;

Cerebral flow index (CFI) = CPP/RAP [18]

All data were analyzed using the SAS® version 9.3 software (SAS Institute, Cary, NC, USA) with significance of two-tailed tests set at < 5%. The comparisons of statistically significant differences between normal and PE groups were made using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Transcranial Doppler values were assessed using a logistic regression model after adjustments for maternal age and body mass index (BMI) because high BMI is correlated with reduced cerebral blood flow velocities and increased cerebrovascular resistance.[19]. To assess the performance indices of the TCD parameters, optimal cut-off values with the largest area under curve (AUC) were estimated using the receiver operating characteristic (ROC) curve. The PE group was then divided into two subgroups according to presence of cerebral symptoms such as headache or visual disturbance and the differences in parameters were analyzed between the two groups. The headaches originating from PE was decided according to diagnostic criteria of the international classification of headache disorder 3 (ICHD-3) of international headache society (IHS) [20]. Visual changes of PE were diagnosed as the following symptoms after pregnancy: blurred vision, flashing lights or sparks, scotomata [16].

3. Results

In this comparison of normal and PE pregnancies, mean age, BMI, systolic and diastolic BP, mean BP and cesarean delivery rate were significantly higher in the PE group, whereas gestational age at the time of TCD, gravidity, and parity did not differ significantly (Table 1). Thus, maternal age and BMI were calibrated for the adjustment of TCD indices using the logistic regression model. Before overall analyzing of the TCD values between PE and normal pregnancies, we performed multiple comparison subgroup analysis according to administration of drugs that could affect cerebral blood flow and these results were similar to overall analysis (Table 2). PI and RI values were significantly lower and CPP and RAP were significantly higher in the PE group ($P < 0.05$). MCV and CFI were significantly increased in only PCA of the PE group ($P = 0.040$ and 0.028, respectively) (Table 2). The results of a comparative analysis in PE women classified according to the presence of symptoms are summarized in Table 3. Unlike other TCD indices, it is noteworthy that CPP and RAP of PCA in the symptomatic group were significantly higher than in the non-symptomatic group ($P < 0.05$).

The performance indices of TCD parameters were analyzed using ROC-AUC values for predicting PE-related cerebral symptoms (Fig. 2, Table 4). With respect to the PI and RI parameters, MCA had the highest sensitivities (91.7%, 85.4%) at values < 0.75 and < 0.50, respectively, while cut-off values of the PCA ≤ 0.70 and ≤ 0.49 had the highest specificities (95.0%, 90.0%). The highest likelihood ratio was shown less than < 0.70 in the PI of PCA (14.58). Thus, both MCA and PCA

Table 1
Characteristics of normal and PE pregnancy women.

	Normal (n = 20)	PE (n = 48)
*Mean age (years)	29.50 [28.75–31.00]	34.00 [30.75–37.00]
GA at TCD (weeks)	30.50 [29.82–31.43]	32.86 [29.25–34.89]
Gravidity	1.50 [1.00–2.25]	2.00 [1.00–3.00]
Parity	0.00 [0.00–1.00]	0.00 [0.00–1.00]
*Pre-pregnancy BMI (kg/m^2)	20.10 [17.72–23.11]	22.99 [20.80–26.31]
*Systolic BP	110.00 [100.00–110.00]	140.00 [140.00–152.50]
*Diastolic BP	70.00 [60.00–70.00]	90.00 [90.00–100.00]
*Mean BP	83.33 [73.33–83.33]	110.00 [105.83–117.50]
Urine protein (mg/24 h)	NA	1697.95 [917.43–4310.92]
*Cesarean delivery	11 (55.0%)	35 (87.5%)
*Birth weight of newborn (g)	2745.00 [2400.00–2995.00]	1815.00 [122.75–2250.00]

Values are presented as median [interquartile range]. *P value < 0.05. BMI: body mass index; BP: blood pressure; GA: gestational age; NA: not assessed; PE: preeclampsia; TCD: transcranial Doppler.

Table 2
TCD indices of normal and PE pregnancy women.

		Normal (n = 20)	PE (n = 48)	P
MCV (cm/s)	ACA	49.50 [45.50–54.50]	51.00 [39.00–63.00]	0.995
	MCA	78.00 [66.25–90.50]	79.00 [65.75–90.75]	0.623
	PCA	38.00 [34.50–41.25]	41.00 [37.75–50.00]	0.040
PI	ACA	0.87 [0.79–0.98]	0.69 [0.64–0.76]	0.001
	MCA	0.91 [0.80–1.03]	0.68 [0.61–0.75]	0.001
	PCA	1.00 [0.82–1.12]	0.67 [0.61–0.79]	0.001
RI	ACA	0.57 [0.53–0.60]	0.49 [0.47–0.53]	0.001
	MCA	0.57 [0.53–0.60]	0.49 [0.45–0.51]	0.001
	PCA	0.61 [0.54–0.63]	0.48 [0.44–0.54]	0.001
CPP	ACA	48.09 [42.19–53.33]	70.09 [53.33–78.55]	0.001
	MCA	47.12 [44.05–54.69]	68.89 [54.83–80.61]	0.001
	PCA	46.36 [43.06–48.47]	68.88 [58.80–83.50]	0.001
RAP	ACA	1.36 [1.08–1.44]	1.87 [1.54–2.26]	0.001
	MCA	1.20 [1.05–1.39]	1.55 [1.31–1.80]	0.001
	PCA	2.76 [2.37–3.00]	3.29 [2.58–3.78]	0.012
CFI	ACA	24.93 [21.38–32.32]	27.54 [19.14–33.74]	0.968
	MCA	41.41 [35.11–54.27]	46.34 [34.68–58.67]	0.518
	PCA	19.97 [18.24–24.42]	24.45 [19.70–29.72]	0.028

Values are presented as median [interquartile range]. ACA: anterior cerebral artery; CFI: cerebral flow index; CPP: cerebral perfusion pressure; MCA: middle cerebral artery; MCV: mean cerebral velocity; PCA: posterior cerebral artery; PE: preeclampsia; PI: pulsatility index; RAP: resistance area product; RI: resistance index; TCD: transcranial Doppler.

Table 3
TCD indices by cerebral symptom status in PE pregnancies.

		No symptoms (n = 26)	Cerebral symptoms (n = 22)	P
MCV (cm/s)	ACA	46.00 [39.00–65.25]	53.00 [45.25–61.75]	0.844
	MCA	79.00 [65.25–99.25]	78.50 [67.50–85.75]	0.431
	PCA	41.50 [37.25–50.00]	41.00 [38.00–48.25]	0.462
PI	ACA	0.70 [0.61–0.74]	0.68 [0.65–0.77]	0.756
	MCA	0.66 [0.58–0.74]	0.69 [0.63–0.75]	0.363
	PCA	0.63 [0.59–0.76]	0.70 [0.67–0.79]	0.109
RI	ACA	0.49 [0.45–0.53]	0.49 [0.47–0.53]	0.844
	MCA	0.48 [0.43–0.51]	0.49 [0.46–0.51]	0.469
	PCA	0.47 [0.44–0.52]	0.50 [0.46–0.54]	0.159
CPP	ACA	64.85 [52.83–76.52]	71.25 [56.18–83.51]	0.108
	MCA	63.96 [51.91–78.49]	73.89 [64.33–90.55]	0.056
	PCA	63.30 [55.37–79.50]	77.90 [62.78–87.05]	0.036
RAP	ACA	1.85 [1.45–2.23]	1.89 [1.61–2.24]	0.605
	MCA	1.48 [1.19–1.72]	1.63 [1.47–1.92]	0.066
	PCA	2.99 [2.47–3.56]	3.60 [2.87–3.96]	0.030
CFI	ACA	26.82 [18.88–32.31]	28.58 [24.41–34.63]	0.495
	MCA	46.48 [34.39–56.53]	45.86 [37.14–61.80]	0.926
	PCA	23.20 [19.83–31.82]	26.32 [19.61–29.11]	0.893

Values are presented as median [interquartile range]. ACA: anterior cerebral artery; CFI: cerebral flow index; CPP: cerebral perfusion pressure; MCA: middle cerebral artery; MCV: mean cerebral velocity; PCA: posterior cerebral artery; PE: preeclampsia; PI: pulsatility index; RAP: resistance area product; RI: resistance index; TCD: transcranial Doppler.

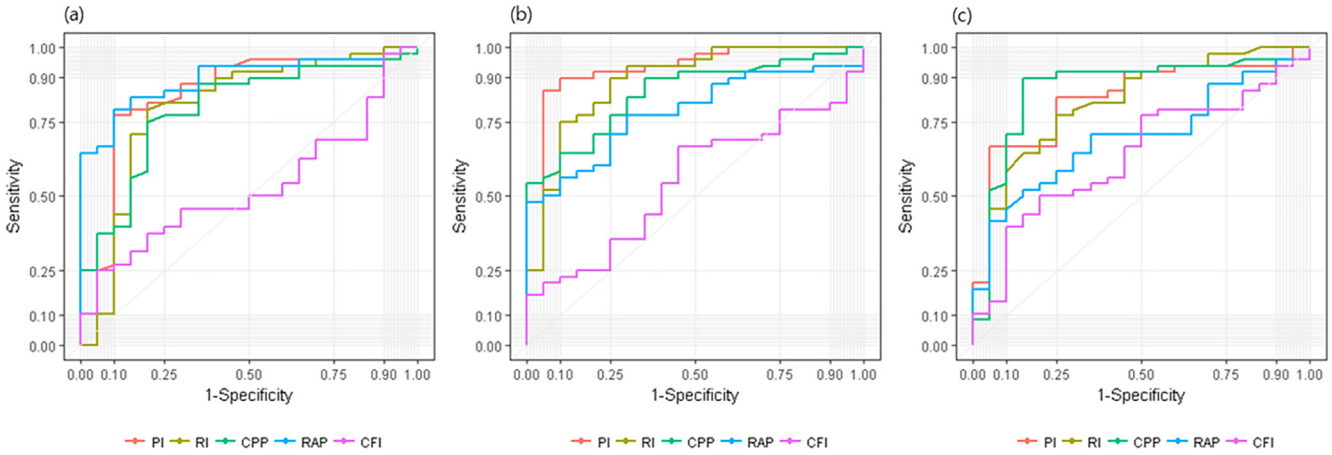

Fig. 2. ROC curve of performance indices of TCD. ROC curve of ACA, MCA, and PCA for performance indices associated with PE (a, b, c). ACA: anterior cerebral artery; CFI: cerebral flow index; CPP: cerebral perfusion pressure; MCA: middle cerebral artery; MCV: mean cerebral velocity; PCA: posterior cerebral artery; PE: preeclampsia; PI: pulsatility index; RAP: resistance area product; ROC: receiver operating characteristic; RI: resistance index; TCD: transcranial Doppler.

were clinically meaningful in the PI and RI. As the CPP value reflecting the degree of cerebral autoregulation in PE women, PCA had the highest sensitivity, specificity, and positive likelihood ratio (89.6%, 85.0%, and 5.97, respectively) when it exceeded 48.70. RAP had the highest sensitivity and specificity in ACA (79.2% and 90.0%, respectively). Compared to other parameters, CFI showed relatively low sensitivity in the PCA (52.1%).

4. Discussion

As previously mentioned, cerebral complications associated with PE contribute to serious maternal morbidity and mortality. Therefore, for prediction of PE and assessment of brain injuries, some investigations have been conducted studies using TCD indices of the cerebral arteries. Riskin-Masiah et al. reported a decrease of PI and RI in the TCD test before the onset of overt PE in normotensive women, and that PE could be predicted from these results. Belfort et al. published that PE could be predicted at 86% sensitivity and 93% specificity for a PI < 0.81 and RI < 0.54 of TCD in the normotensive pregnancy group in the second trimester [12,21]. Further, in these studies, we analyzed TCD parameters of PCA to predict cerebral symptoms in PE pregnancies. Although our study design is differs from these researches, PI and RI were lower in the PE group and the sensitivity and specificity were the highest or relatively high when the PI and RI of MCA values were < 0.75 and < 0.50, similarly. However, highest specificity and likelihood ratio were obtained in PI of PCA < 0.70 (95.0%, 14.58). This result suggested that PCA could be associated with cerebral symptoms in PE women. Lowering of the PI and RI maintains cerebral perfusion pressure and protects the cerebral blood flow (CBF) from vasospasm. In the analysis of MCA in the previous study, CPP was elevated and CFI remained within the normal range to maintain sufficient cerebral blood flow when abnormal cerebral vasospasm occurred in PE pregnancies [22]. However, here we noted a statistically significant increase in CFI of the PCA (Table 2). In the women with eclampsia, the persistent elevated BP and abnormally increased CPP results in cerebrovascular barotrauma, including endothelial damage and blood–brain barrier disruption. Eventually, these cerebral overperfusion injuries lead to an increase in CBF above the normal range. Similar to this mechanism, increased CPP and CBF were observed in severe PE pregnancies significantly and these women more tended to develop neurologic complication. [23]. In the current study, CFI, which reflects CBF, was significantly higher in the PCA than MCA in PE pregnancies. This result suggests that the PCA better reflected cerebral overperfusion injury than the MCA in PE pregnancies. Therefore, the change of CFI in the PCA is a notable finding with TCD, considering that the abnormal brain lesions of PE women was confined to the occipital lobe in a recent

Table 4
Performance indices of TCD parameters for predicting PE related cerebral symptoms.

		Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
PI	ACA	≤0.73	83.1	90.0	95.3	69.2	8.33	0.19
	MCA	≤0.75	91.7	90.0	95.7	82.6	9.17	0.09
	PCA	≤0.70	72.9	95.0	95.0	62.1	14.58	0.26
RI	ACA	≤0.50	79.2	80.0	90.7	61.9	3.96	0.26
	MCA	≤0.50	85.4	85.0	93.3	71.4	5.69	0.17
	PCA	≤0.49	77.1	90.0	90.7	61.9	7.70	0.25
CPP	ACA	> 52.25	81.2	80.0	90.9	64.0	4.06	0.23
	MCA	> 48.71	87.5	70.7	87.5	70.5	2.92	0.18
	PCA	> 48.70	89.6	85.0	93.5	77.3	5.97	0.12
RAP	ACA	> 1.42	79.2	90.0	95.1	64.3	7.92	0.23
	MCA	> 1.48	58.3	95.0	96.7	48.8	11.67	0.44
	PCA	> 2.70	68.8	80.0	89.5	51.6	3.44	0.39
CFI	ACA	> 28.27	35.4	90.9	90.0	36.7	3.54	0.72
	MCA	> 42.80	60.4	65.0	80.6	40.6	1.73	0.61
	PCA	> 22.17	52.1	85.0	89.6	42.5	3.47	0.56

ACA: anterior cerebral artery; CFI: cerebral flow index; CPP: cerebral perfusion pressure; MCA: middle cerebral artery; MCV: mean cerebral velocity; LR: likelihood ratio; PCA: posterior cerebral artery; PE: preeclampsia; PI: pulsatility index; RAP: resistance area product; RI: resistance index; TCD: transcranial Doppler.

imaging modality study [24]. As mentioned above, the hypertension or fluctuations of BP could cause excess of cerebral perfusion pressure. However, cerebrovascular pressure reactivity and autonomic nervous system maintain constant cerebral blood flow: cerebral autoregulation. Fischer et al. presented the cerebral occipital lobe has little density of nerve sympathetic innervation compared to anterior or middle cerebral circulation, which reduced control of cerebral autoregulation in severe hypertension [25]. This pathophysiology could explain the reason of CFI was significantly elevated in only PCA. However, additional physiological and anatomical considerations are needed to clarify the reason that these results are particularly prominent in the PCA. In order to complement such a point, we subdivided the PE group according to the presence of cerebral symptoms, and analyzed the TCD parameters (Table 3).

It is well known that cerebral symptoms such as persistent headache, visual disturbance, and photophobia manifest before seizure in eclamptic pregnant women [26]. These symptoms are suspected to be correlated with the severities of vasogenic brain edema caused by cerebrovascular overperfusion in the cerebral circulation of the bilateral parietooccipital region and this could be clinically defined posterior reversible encephalopathy syndrome (PRES) [27]. According to a report of Mayama et al. in 2016, indications for PRES were observed in symptomatic PE patients (19.2%) [28]. Based on correlation of cerebral symptoms with posterior lobe changes, we focused this study to evaluate TCD parameters in PCA of PE pregnancies. As a result, our data suggests that the development of cerebral symptoms in PE patients is associated with pathological alteration of the PCA hemodynamics. CPP, RAP, and CFI values increased in all three cerebral vessels in the cerebral symptom group, but statistically significant differences were seen in the CPP and RAP values of the PCA. This significant increase in parameters associated with PCA may suggest that TCD measurements in PCA could be more useful for evaluating cerebral overperfusion in symptomatic women with PE pregnancies. This is the strength of this study, as previous studies have mainly studied the TCD parameters of the MCA [29,30]. If we compare TCD values with other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) used in previous PRES studies, it may be helpful to establish the correlation of the changes in TCD parameters of the PCA with PRES.

In normal pregnancy, as gestational age increases, changes in the cerebral hemodynamics occur such as decreased velocity, PI and RI of the MCA, and increased CPP [31]. These changes eventually maintain brain homeostasis by functionally enhancing cerebral autoregulation [32]. Considering these changes during pregnancy, if more pregnant women are included and compared by gestational age in further research, more reliable results can be obtained. Magnesium sulfate ($MgSO_4$) has multifactorial actions to prevent eclampsia-related seizure. It has a vasodilatory effect on the cerebral vessels and decreases tight junction permeability in the cerebral endothelium to maintain the blood–brain barrier, which limits the development of cerebral edema [33]. In this study, 14 pregnant women underwent a TCD test after $MgSO_4$ administration. In further study, we should be adjusted for the cerebral vasodilatation effect of $MgSO_4$ in such women.

In conclusion, analysis of maternal TCD of a PCA could be a novel parameter associated with a symptomatic PE pregnant women. We may be able to set the optimal cut-off value for predicting cerebral symptoms associated with dysfunction of cerebral autoregulation by comparing these PCA parameters in a larger cohort of women with PE in future research.

Conflict of interest

The authors report no conflicts of interest.

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