

OBSTETRICS

Cerebral perfusion pressure and autoregulation in eclampsia—a case control study



Lina Bergman, MD, PhD; Catherine Cluver, MD, PhD; Niclas Carlberg, MD; Michael Belfort, MD, PhD; Mary C. Tolcher, MD, MSc; Ronney B. Panerai, MD, PhD; Teelkien van Veen, MD, PhD

BACKGROUND: Dynamic cerebral autoregulation and cerebral perfusion pressure are altered in pregnancies complicated by preeclampsia compared with normotensive pregnancies, but the connections of dynamic cerebral autoregulation, cerebral perfusion pressure, and cerebral complications in preeclampsia remain unclear.

OBJECTIVE: This study aimed to assess dynamic cerebral autoregulation and cerebral perfusion pressure after delivery in women with eclampsia, in women with preeclampsia both with and without severe features, and in normotensive women.

STUDY DESIGN: This was a prospective case control study at a large referral hospital in Cape Town, South Africa. The recruitment of participants was done at diagnosis (cases) or at admission for delivery (controls). Transcranial Doppler examinations with continuous noninvasive blood pressure measurements and end-tidal CO₂ monitoring were conducted for cases and controls after delivery. Cerebral perfusion pressure and dynamic cerebral autoregulation index were calculated, and values were compared among groups.

RESULTS: We included 16 women with eclampsia, 18 women with preeclampsia with severe features, 32 women with preeclampsia without severe features, and 21 normotensive women with uncomplicated pregnancies. Dynamic cerebral autoregulation was depressed in pregnant women with eclampsia; (autoregulation index, 3.9;

interquartile range, 3.1–5.2) compared with all other groups (those with preeclampsia with severe features, autoregulation index, 5.6 [interquartile range, 4.4–6.8]; those with preeclampsia without severe features, autoregulation index, 6.8 [interquartile range, 5.1–7.4]; and normotensive controls, autoregulation index, 7.1 [interquartile range, 6.1–7.9]). Pregnant women with eclampsia had increased cerebral perfusion pressure (109.5 mm Hg; interquartile range, 91.2–130.9) compared with those with preeclampsia without severe features and those with normal blood pressure (84 mm Hg [interquartile range, 73.0–122.0] and 80.0 mm Hg [interquartile range, 67.5–92.0], respectively); furthermore, there was no difference in cerebral perfusion pressure between pregnant women with eclampsia and pregnant women with preeclampsia with severe features (109.5 mm Hg [interquartile range, 91.2–130.9] vs 96.5 mm Hg [interquartile range, 75.8–110.5]).

CONCLUSION: Cerebral perfusion pressure and dynamic cerebral autoregulation are altered in eclampsia and may be important in the pathophysiological pathway and constitute a therapeutic target in the prevention of cerebral complications in preeclampsia.

Key words: cerebral autoregulation, cerebral blood flow, cerebral perfusion pressure, preeclampsia

Introduction

Preeclampsia (PE), defined as hypertension with end-organ dysfunction after 20 weeks of gestation, is a multisystem disorder that complicates 4% to 6% of all pregnancies.^{1,2} Cerebral complications, which include convulsions, cerebral edema, and hemorrhage, often result in severe maternal morbidity and mortality.³ Long-term neurologic effects of PE and its complications include an increased risk of white matter lesions, stroke, seizure disorders, and vascular dementia later in life.^{4–6}

The underlying pathophysiological mechanism of cerebral complications in PE has not been fully elucidated. Endothelial dysfunction at the blood-brain barrier level along with or resulting in cerebral blood flow alteration is a leading theory.⁷ Studies using transcranial Doppler (TCD) ultrasound have consistently shown increased cerebral perfusion pressure (CPP) in PE, although with large variances within groups.^{8–11} Dynamic cerebral autoregulation (DCA) is a physiological process that maintains cerebral blood flow relatively constant despite changes in blood pressure (BP). Altered DCA may cause over- or underperfusion injury and subsequent cerebral edema. Using TCD ultrasound and continuous BP measurement, DCA has been shown to be depressed in pregnant women with PE compared with those with normal BP.¹¹ It is not known whether CPP or

DCA has a direct role in the development of cerebral complications of PE, including cerebral edema and eclamptic convulsions, and whether CPP or DCA differs concerning severity of disease.

Here, we aimed to assess whether pregnant women with eclampsia demonstrate a less effective DCA and have different CPP than those with other phenotypes of PE (PE with and without severe features (SFs) excluding eclampsia) and those with normal BP.

Materials and Methods

Ethical approval was obtained (protocol number N18/03/034, Federalwide Assurance number 00001372, institutional review board number IRB0005239), and all participants submitted a signed informed consent before being enrolled in the Preeclampsia Obstetric Adverse Events (PROVE) biobank.

Cite this article as: Bergman L, Cluver C, Carlberg N, et al. Cerebral perfusion pressure and autoregulation in eclampsia—a case control study. *Am J Obstet Gynecol* 2021;225:185.e1-9.

0002-9378

© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).
<https://doi.org/10.1016/j.ajog.2021.03.017>

AJOG at a Glance

Why was this study conducted?

This study aimed to assess whether depressed dynamic cerebral autoregulation (DCA) may be a part of the pathophysiological pathway to cerebral edema and eclampsia.

Key findings

Women with pregnancies complicated by eclampsia demonstrated the least effective autoregulation, followed by pregnant women with preeclampsia (PE) with severe features (SFs) and then pregnant women with PE without SFs.

What does this add to what is known?

Although there are studies demonstrating depressed DCA in PE, it is not known whether depressed DCA is associated with cerebral complications in PE. This study showed that depressed DCA may be an important pathophysiological mechanism in the pathophysiology of cerebral edema and eclampsia in pregnancies complicated by PE.

Population

We included pregnant women with PE and pregnant women with normal BP who were recruited to the PROVE biobank and database at Tygerberg Hospital, Cape Town, South Africa. The PROVE biobank is an ongoing collaborative project facilitating research in the field of PE. Tygerberg Hospital is the largest referral hospital in the Western Cape Province of South Africa. In 2018, there were 32,422 deliveries in the referral area, of which 8067 were considered high risk and delivered at Tygerberg. The PROVE biobank includes mostly pregnant women with eclampsia, and about 50 pregnant women with eclampsia are recruited yearly.

Here, we included only women with singleton pregnancy. Exclusion criteria included known neurologic or cardiac disease. For normotensive women, additional exclusion criteria were chronic hypertension and diabetes mellitus. All women were examined within 5 days of delivery, with most women examined within 48 hours. PE was defined according to the American College of Obstetricians and Gynecologists (ACOG) 2019 Practice Bulletin.¹² Eclampsia was confirmed when PE was complicated by witnessed generalized tonic-clonic seizures in the absence of another etiology. Pulmonary edema was diagnosed when there was worsening

dyspnea, bibasilar inspiratory crackles on auscultation, and features of pulmonary edema on chest x-ray. Hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome) and PE without SFs were diagnosed in accordance with the ACOG Practice Bulletin.¹² A woman was considered normotensive if she had no documented systolic BP of ≥ 140 mm Hg or a diastolic BP of ≥ 90 mm Hg during her pregnancy.

Baseline data were obtained by interview and extraction from medical records. All data were entered and stored using Research Electronic Data Capture tools hosted at Stellenbosch University.¹³ Data were double-checked for accuracy and audited with original data collection forms.

Dynamic cerebral autoregulation and cerebral perfusion pressure

The examination was conducted after delivery in all women. At the time of TCD examination, noninvasive brachial systolic and diastolic BPs were measured. With the women in supine or semi-Fowler's position, maternal TCD interrogation of the middle cerebral artery was conducted using a 2-MHz pulsed, range gated TCD probe (Spencer Technologies, Seattle, WA), held in place using a headframe. Measurements were done bilaterally if possible.

BP was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, the Netherlands) with the servo-adjust switched off and was postfacto calibrated with the brachial BP. In addition, BP tracing served to mark each cardiac cycle. End-tidal CO₂ (EtCO₂) was measured using a nasal cannula (Nellcor OxiMax N-85, Covidien, Mansfield, MA) and linearly interpolated at the end of each expiratory phase.

TCD measurements were made during a single 7-minute episode, and spontaneous fluctuations in systemic BP were used when calculating the autoregulation index (ARI). All data were recorded at 50 Hz, interpolated to 200 Hz, and visually inspected during analysis to remove large spikes. A median filter was used to remove small spikes and artifacts in the cerebral blood flow velocity (CBFV) signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, EtCO₂, and heart rate were then calculated for each beat.¹⁴ The reported CBFV and CPP values were the average values over the 7-minute baseline recording.

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP as described previously.¹⁴ Segments of 512 samples and 50% superposition were transformed with the fast Fourier (FFT) algorithm, using the Welch method to obtain the transfer function parameters (coherence, gain, and phase shift) in the very low-frequency (VLF) range (0.02–0.07 Hz), where DCA is most active, and in the low-frequency (LF) range (0.07–0.20 Hz).¹⁵

The inverse FFT was then used to estimate the impulse and step responses. The CBFV step response to a sudden change in BP was compared with 10 template curves proposed by Tiecks et al,¹⁶ and the best-fit curve corresponded to the ARI. A value of ARI=9 represents the best observed cerebral autoregulation, whereas a value of ARI=0 corresponds to absence of DCA. Measurements were rejected if mean

coherence function was <0.19 and when the normalized mean square error for fitting the step response was >0.30 .¹⁶

CPP was calculated using the averages of the velocity and maternal BP data as follows: $CPP = [\text{velocity}_{\text{mean}} / (\text{velocity}_{\text{mean}} - \text{velocity}_{\text{diastolic}})] (\text{mean arterial BP} - \text{diastolic BP})$.¹⁰

Statistics

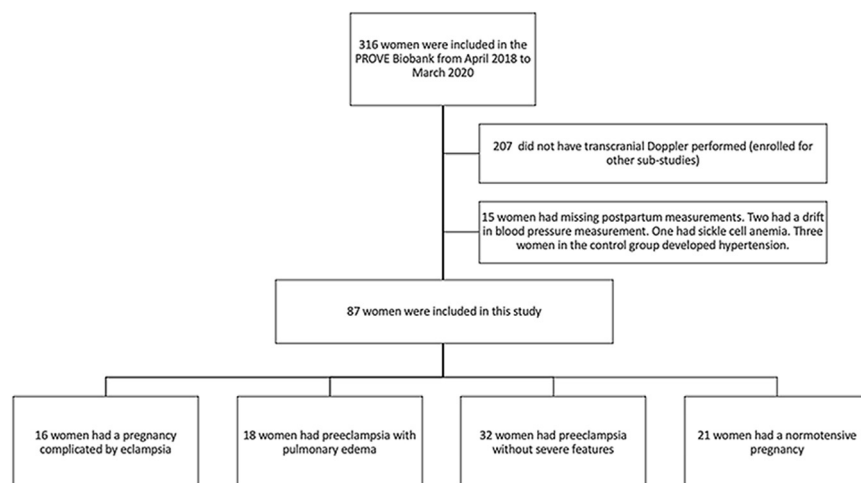
Demographic and clinical characteristics were presented as means with standard deviations (SDs) and percentages and were compared among groups by analysis of variance and chi-square tests. ARI, CPP, and transfer function analyses (TFA) variables were presented as medians with interquartile range (IQR) and compared among groups using the Kruskal-Wallis test and for ARI and CPP pairwise comparisons with Mann-Whitney *U* test and Bonferroni correction. In all hypothesis tests, a *P* value of $<.05$ was considered statistically significant. Data and statistical analyses were performed using Statistical Package for Social Sciences Statistics (version 26.0; SPSS Inc, Chicago, IL) for MAC software package (Apple Inc, Cupertino, CA).

To detect a difference in ARI between women with PE and women with normal BP, a sample size of 32 in each group was required on the basis of a previous publication with a difference of 1.2 with an SD of 1.7.¹¹ We estimated that the difference in ARI would be 1.7 between women with eclampsia and women with normotensive pregnancy with an SD of 1.7. The sample size for a between-group difference was set at 16 women with eclampsia and at least an equal number of women in the control group.

Results

This study was conducted from April 2018 to March 2020 during which time 316 women were included in the PROVE biobank. Of these women, 109 women had assessment of DCA. The study population is described in Figure 1. Women were excluded because of missing postpartum measurement ($n=15$), drift of the BP signal ($n=2$), too much noise in the TCD measurement ($n=5$), sickle cell anemia ($n=1$), or development of hypertension following

FIGURE 1
Flowchart of the study population



PROVE, Preeclampsia Obstetric Adverse Events.

Bergman et al. Depressed dynamic cerebral autoregulation in eclampsia. *Am J Obstet Gynecol* 2021.

inclusion in the control group ($n=3$). Of the 87 women included in the study, 16 had eclampsia, 18 had PE with SFs, 32 had PE without SFs, and 21 had normal BP during pregnancy.

Background characteristics

Maternal characteristics and pregnancy outcomes are presented in Table 1. Compared with the other groups, women with eclampsia were generally younger, more commonly nulliparous, and more likely to smoke and use alcohol. In the group of women with PE with SFs, 7 (39%) had HELLP syndrome, 9 (50%) had pulmonary edema, and 3 (17%) had renal impairment. In the group of women with eclampsia, the corresponding numbers were 1 (6%) for HELLP syndrome, pulmonary edema, and renal impairment, respectively.

At time of TCD examination, all women with eclampsia had either previous or current treatment with magnesium sulfate compared with 93% of women with PE with SFs and 76% of women with PE without SFs. Furthermore, 2 women (10%) with normal BP had undergone treatment with magnesium sulfate for fetal neuroprotection because of threatened preterm labor. In addition, 94% of women with eclampsia or PE were on

antihypertensive medications at the time of examination.

Dynamic cerebral autoregulation

ARI was measured on the left side, the right side, or bilaterally, depending on where the signal could be best determined. If both sides were recorded, the mean ARI was calculated, and if not, either the left or right side was registered. In Table 2, both recordings from the left and right sides are presented in addition to the pooled value, including missing values. Women with eclampsia demonstrated a lower ARI (3.9; IQR, 3.1–5.2), reflecting less effective DCA, compared with all other groups (PE with SFs, ARI, 5.6 [IQR, 4.4–6.8]; PE without SFs, ARI, 6.8 [IQR, 5.1–7.4]; and normotensive controls, ARI, 7.1 [IQR, 6.1–7.9]). Pairwise comparisons among groups are presented in Figure 2, A. Deterioration of cerebral autoregulation in the eclampsia group was confirmed by the reduced values of TFA phase shift for the VLF band (Supplemental Table).

There was no difference in ARI among women with PE with SFs, women with PE without SFs, and normotensive controls after Bonferroni correction (Figure 2, A). Similar to the ARI, phase shift, gain, and coherence were not different for these groups (Supplemental Table).

TABLE 1
Maternal characteristics and pregnancy outcomes of the study population

Characteristic	Eclampsia	Preeclampsia with severe features	Preeclampsia without severe features	Normal pregnancy
n	16	18	32	21
At baseline				
Maternal age (y)	23.5 (5.9)	29.0 (6.2)	29.4 (7.2)	29.8 (6.8)
Race				
Black	8 (50)	12 (67)	21 (66)	13 (62)
Mixed race	8 (50)	6 (33)	10 (31)	8 (38)
White	0 (0)	0 (0)	1 (3)	0 (0)
Nulliparous	10 (63)	7 (44)	10 (31)	5 (24)
HIV	1 (6)	6 (33)	4 (13)	4 (19)
Smoking	4 (27)	0 (0)	3 (9)	2 (10)
Missing	1 (6)	2 (11)	0 (0)	1 (5)
Alcohol use	3 (20)	0 (0)	1 (3)	0 (0)
Missing	1 (6)	2 (11)	0 (0)	1 (5)
Methamphetamine use	0 (0)	0 (0)	1 (3)	0 (0)
Missing	1 (5)	0 (0)	0 (0)	2 (10)
Diabetes mellitus	—	—	2 (7)	2 (9)
Pregestational	0 (0)	0 (0)	1 (3)	1 (5)
Pregnancy induced	1 (5)	1 (6)	1 (3)	1 (5)
Chronic hypertension	1 (6)	3 (17)	9 (28)	0 (0)
Neurologic disease	0 (0)	0 (0)	0 (0)	0 (0)
BMI (kg/m ²)	25.2 (3.4)	28.5 (8.4)	29.4 (6.1)	27.3 (9.5)
Missing	1 (6)	3 (17)	2 (6)	2 (10)
At delivery				
GA at delivery (wk)	34.3 (4.3)	32.8 (4.5)	34.1 (4.0)	36.8 (3.8)
Missing (%)	0 (0)	0 (0)	1 (3)	0 (0)
Mode of delivery				
Vaginal delivery	3 (19)	2 (13)	7 (22)	4 (19)
Elective CD	0 (0)	1 (6)	2 (6)	14 (67)
Emergency CD	13 (81)	13 (81)	23 (72)	3 (14)
Liveborn	16 (100)	16 (89)	31 (97)	21 (100)
Missing	0 (0)	0 (0)	1 (3)	0 (0)
Birthweight (g)	2096 (764)	1754 (826)	2176 (887)	2880 (873)
Missing	0 (0)	1 (6)	0 (0)	0 (0)
Complications				
HELLP syndrome	1 (6)	7 (39)	0 (0)	0 (0)
Pulmonary edema	1 (6)	9 (50)	0 (0)	0 (0)
Renal impairment ^a	1 (6)	3 (17)	0 (0)	0 (0)

Bergman et al. Depressed dynamic cerebral autoregulation in eclampsia. Am J Obstet Gynecol 2021.

(continued)

TABLE 1

Maternal characteristics and pregnancy outcomes of the study population (continued)

Characteristic	Eclampsia	Preeclampsia with severe features	Preeclampsia without severe features	Normal pregnancy
At TCD examination				
Mean arterial BP (mm Hg)	103.6 (17.7)	103.4 (12.4)	108.7 (14.6)	88.9 (8.6)
Magnesium sulfate				
No	0 (0)	1 (7)	7 (24)	19 (91)
Finished treatment	4 (25)	5 (33)	10 (35)	2 (10)
Current treatment	12 (75)	9 (60)	12 (41)	0 (0)
Missing (%)	0 (0)	3 (17)	3 (9)	0 (0)
Hb (g/dL)	10.9 (2.3)	10.3 (1.8)	11.4 (1.6)	10.7 (1.6)
Missing	0 (0)	3 (17)	1 (3)	0 (0)
BP treatment				
None	1 (6)	1 (6)	2 (6)	20 (95)
Oral	7 (44)	9 (50)	22 (69)	1 (0)
Intravenous and oral	8 (50)	8 (44)	8 (25)	0 (0)
ETCO ₂ (mm Hg)	33.6 (32.8–35.6)	34.3 (30.3–35.6)	34.8 (33.0–36.4)	33.6 (32.4–36.2)

Data are presented as mean (standard deviation), median (interquartile range), or number (percentage).

BMI, body mass index; BP, blood pressure; CD, cesarean delivery; ETCO₂, end-tidal carbon dioxide; GA, gestational age; HELLP, hemolysis, elevated liver enzymes, and low platelet count.

^a Creatinine >120 μmol/L.

Bergman et al. Depressed dynamic cerebral autoregulation in eclampsia. *Am J Obstet Gynecol* 2021.

Cerebral perfusion pressure

The CPP was also measured on the left side, the right side, or bilaterally, depending on where the signal could be best recorded. If both sides were recorded, the mean CPP was calculated, and if not, either the left or right side was registered. In Table 2, both recordings from the left and right sides are presented in addition to the pooled value, including missing values. Women with eclampsia demonstrated an increased CPP (109.5 mm Hg; IQR, 91.2–130.9) compared with women with PE without SFs and women with normal BP (84 mm Hg [IQR, 73.0–122.0] and 80.0 mm Hg [IQR, 67.5–92.0], respectively). There was no difference between women with eclampsia and women with PE with SFs (109.5 mm Hg [IQR, 91.2–130.9] vs 96.5 mm Hg [IQR, 75.8–110.5]).

There was no difference in CPP among women with PE with SFs, women with PE without SFs, and normotensive controls after Bonferroni correction (Figure 2, B).

Comment

Principal findings

Here, we found depressed DCA in women with eclampsia compared with those with PE (both with and without SFs) and normotensive controls. Women with eclampsia also demonstrated increased CPP; however, the difference was only present when compared with women with less severe disease and normotensive controls and did not hold true when compared with women with PE with SFs.

Results in context

It has previously been demonstrated that women with PE have depressed DCA compared with women with normal BP during pregnancy.¹¹ Here, we chose to use the same method to calculate DCA and CPP to be able to compare our results. Notably, it is a safe method without discomfort for the study participant.¹⁷ Our results complement this by showing that PE with evidence of neurologic impairment (ie, eclampsia) is

associated with even less effective DCA, as shown by both ARI and the phase shift in the VLF range, than PE without neurologic impairment, despite BP being similar in these groups. This association supports the theory that depressed DCA may contribute to cerebral complications, such as cerebral edema, seizures, and stroke seen in women with PE with SFs. To our knowledge, only a single study on DCA in eclampsia has been published that described a severely reduced phase shift and elevated gain in 2 patients with eclampsia.¹⁸ These changes are highly suggestive of depressed DCA in these patients.

Although rarely applied in obstetrical research, DCA is commonly used to examine the pathophysiology of cerebral blood flow regulation, giving insight to the structural and functional changes of endothelial function, and the smooth muscle response and sensitivity to sympathetic activity.¹⁹ Studies in stroke¹⁹ and traumatic brain injury¹⁷ show results in line with our study: significantly

TABLE 2

Cerebral perfusion pressure and autoregulatory index in the study population

Variable	Eclampsia	Preeclampsia with severe features	Preeclampsia without severe features	Normal pregnancy	P value
n	16	18	32	21	
CPP left (mm Hg)	105.0 (87.0–116.5)	96.6 (70.5–108.6)	89.3 (69.8–111.3)	76.0 (64.0–93.0)	<.05
Missing	3 (19)	2 (11)	10 (31)	6 (29)	
CPP right (mm Hg)	108.8 (89.9–132.5)	97.0 (80.0–107.5)	91.5 (73.0–121.8)	77.0 (68.0–95.0)	<.01
Missing	4 (25)	6 (33)	8 (25)	0 (0)	
CPP mean (mm Hg)	109.5 (91.2–130.9)	96.5 (75.8–110.5)	84.0 (73.0–122.0)	80.0 (67.5–92.0)	<.01
Missing	0 (0)	0 (0)	1 (3)	0 (0)	
ARI left	4.5 (3.2–6.7)	5.6 (4.2–6.4)	6.7 (5.0–7.3)	7.0 (6.4–8.0)	<.05
Missing	3 (19)	2 (11)	10 (31)	8 (38)	
ARI right	3.7 (2.9–4.8)	6.0 (4.4–8.1)	6.7 (3.9–7.6)	7.1 (6.5–7.8)	<.01
Missing	4 (25)	7 (39)	7 (22)	0 (0)	
ARI mean	3.9 (3.1–5.2)	5.6 (4.4–6.8)	6.8 (5.1–7.4)	7.1 (6.1–7.9)	<.001
Missing	0 (0)	0 (0)	0 (0)	0 (0)	

Data are presented as median (interquartile range) or number (percentage). Kruskal-Wallis tests were used for global differences among groups.

ARI, autoregulatory index; CPP, cerebral perfusion pressure.

Bergman et al. Depressed dynamic cerebral autoregulation in eclampsia. *Am J Obstet Gynecol* 2021.

reduced ARI in patients with a stroke compared with controls¹⁹ and a lower ARI in nonsurvivors vs survivors in traumatic brain injury, with ARI being an important variable able to reliably predict outcome.¹⁹

Here, DCA was not different between women with PE and women with normal BP during pregnancy, which is in contrast with earlier findings.¹¹ This is most likely caused by a type 2 error associated with the 4 groups, demanding a larger sample size to achieve the same results, and possibly by a difference in population characteristics, such as ethnicity. The median ARI in our control group was slightly higher than in a previous study (median of 7.1 [IQR, 6.1–7.9] vs a mean of 6.7±0.6 SD),¹¹ and the ARI in all women with PE (with and without SFs combined) was 6.2 (IQR, 4.8–7.2), also higher than previously reported (mean of 5.5±1.7 SD), despite using the same equipment and analysis software.¹¹ In addition, our study was conducted after delivery, whereas earlier studies have examined women before delivery. Because cerebral blood flow is altered in pregnancy, this

might also contribute to the different results in our study.¹¹

Previous studies suggest that women with PE demonstrate an increased CPP compared with normotensive controls, but PE has also been associated with underperfusion (as indicated by CPP and compared with 95% confidence intervals for normal pregnancy): 52% of women with PE without SFs have underperfusion and 59% of women with PE with SFs have overperfusion,²⁰ with women with headache being more likely to have abnormal CPP than those without headache.²¹

In our population, this difference was not statistically significant, perhaps because of the large variances and small sample size. Other explanations could be treatment effects. Magnesium sulfate treatment reduces CPP in women with PE and increase CPP at baseline.¹⁷ In our population, most women with PE and all women with eclampsia had current or previous treatment with magnesium sulfate. Thus, this might have reduced CPP in those groups and reduced the difference between women with PE and normotensive controls. The same

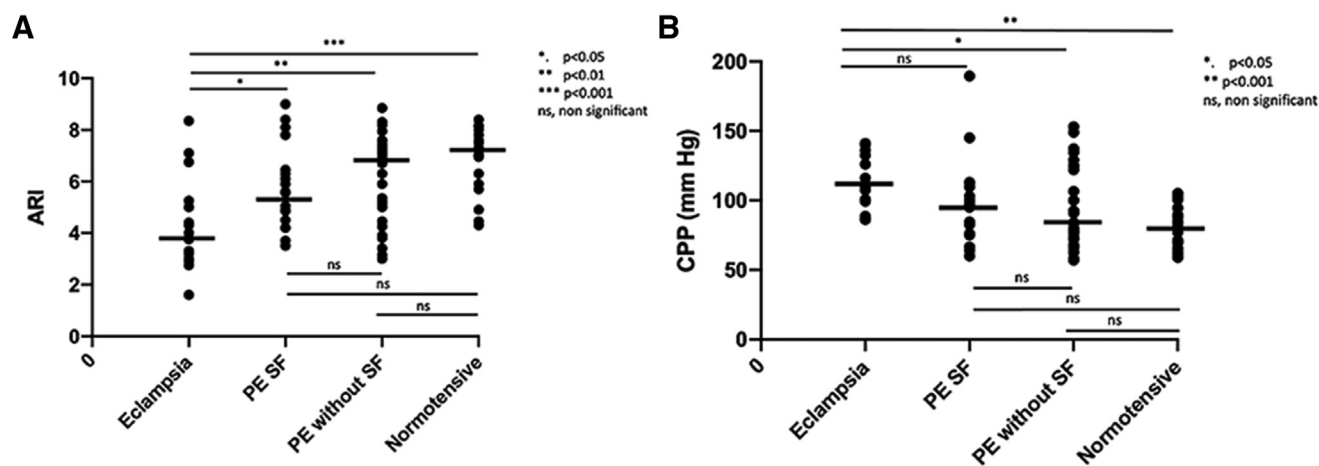
decrease in CPP in PE has also been reported after labetalol and nifedipine administration, medications commonly used in our population of women with eclampsia.²²

Clinical implications

The most common cause of maternal mortality in PE is neurologic catastrophe. Therefore, it is imperative to understand the underlying pathophysiological pathways to cerebral complications in PE. DCA and, to some extent, CPP may add to our understanding of the pathophysiology. Currently, eclampsia and imminent eclampsia are treated with magnesium sulfate.¹² The mechanism of action is not known but is thought to involve actions at the N-methyl-D-aspartate receptor, inhibition of neuroinflammation, and perhaps unspecified effects on the blood-brain barrier.²³ Magnesium sulfate also decreases CPP in PE as discussed above.²⁴ If DCA and CPP are confirmed in future studies to be important in the development of cerebral complications in PE, medications, such as magnesium sulfate, antihypertensive medications,

FIGURE 2

Dynamic cerebral autoregulation and cerebral perfusion pressure in preeclampsia and normotensive pregnancies



A, Dynamic cerebral ARI. **B**, CPP in, Eclampsia PE with SF, PE without SF, and pregnancies with normal blood pressure. Medians are marked in each group. Differences among groups are estimated by Mann-Whitney *U* test with Bonferroni correction.

ARI, autoregulatory index; CPP, cerebral perfusion pressure; PE, preeclampsia; SF, severe feature.

Bergman et al. Depressed dynamic cerebral autoregulation in eclampsia. *Am J Obstet Gynecol* 2021.

and potential new drug targets, could be evaluated with DCA and CPP endpoints. This could accelerate and facilitate the identification of women at risk of cerebral complications and thus decrease maternal morbidity and mortality.

In addition to the short-term complications, women with previous PE suffer from long-term neurologic sequelae, such as stroke, dementia, and epilepsy.^{4–6} Currently, it is not clear which women run the highest risk of developing these late complications. DCA and CPP might also be useful to predict the long-term effects of PE, and future studies should perhaps include a focus on cerebral blood flow regulation and long-term cerebrovascular health following a pregnancy complicated by PE.

In relation to other disorders, such as ischemic heart failure with high risk of later cognitive impairment and ischemic stroke, an ARI of <4 has been considered as severely depressed.^{25,26} In this cohort, none of the women with normotensive pregnancies but almost half of women with eclampsia demonstrated an ARI of <4. Thus, findings of later cognitive impairment in PE and eclampsia could perhaps have an association with ARI

after diagnosis, but this remains to be proven.

Research implications

The incidence rates of PE and eclampsia are affected by geographic, social, and economic differences. This study investigated DCA in this specific sub-Saharan population. The ARIs in both the control group and group of women with PE seem to be higher than previously reported in different populations, although the women in our study were examined after delivery. Whether a baseline population difference exists should be studied in more detail before cohorts from different populations are combined or compared.

Strengths and limitations

This study included a large number of women with severe disease, which enabled us to assess different phenotypes of PE. Performing assessments on women with severe disease, such as eclampsia, are difficult in high-income countries as the incidence is low (approximately 1 in 2000).²⁷ Despite performing this study in a setting where eclampsia is more prevalent and where

we were able to recruit this cohort in a relatively short period, the study remains underpowered to show differences between PE and the other groups. This is unfortunately a common issue in studies on cerebral autoregulation.¹⁹

Another limitation of the study was that all of our measurements were performed after the onset of seizures in women with eclampsia. Thus, depressed DCA might have evolved after the onset of seizures and might not have been present before, although this is unlikely given the progressive effect noted. Conducting measurements before the onset of seizures would be impossible as eclampsia is unpredictable and rare, even in this population.

Conclusions

There is evidence of depressed DCA in eclampsia, and our data suggested a clear “dose-response” effect, with the worst DCA in women with eclampsia and the best DCA in normotensive women. In addition, women with eclampsia demonstrated an increased CPP compared with those with PE without SFs and those with normal BP during pregnancy.

Acknowledgments

We thank all the women who were willing to be enrolled in our study, the staff at Tygerberg Hospital for their support of the research project, and Sonja Schell for recruiting participants and collecting and entering the baseline data. In addition, we thank Lynn Cluff and Natali Talukder for including women and performing TCD measurements.

References

- Mol BWJ, Roberts CT, Thangaratnam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet* 2016;387:999–1011.
- Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of pre-eclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013;170:1–7.
- Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33:130–7.
- Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. *BMJ* 2018;363:k4109.
- Nerenberg KA, Park AL, Vigod SN, et al. Long-term risk of a seizure disorder after eclampsia. *Obstet Gynecol* 2017;130:1327–33.
- McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156:918–30.
- Bergman L, Torres-Vergara P, Penny J, et al. Investigating maternal brain alterations in pre-eclampsia: the need for a multidisciplinary effort. *Curr Hypertens Rep* 2019;21:72.
- Belfort MA, Saade GR, Yared M, et al. Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia. *Am J Obstet Gynecol* 1999;181:402–7.
- Belfort MA, Tooke-Miller C, Allen JC Jr, Dizon-Townson D, Varner MA. Labetalol decreases cerebral perfusion pressure without negatively affecting cerebral blood flow in hypertensive gravidas. *Hypertens Pregnancy* 2002;21:185–97.
- Belfort MA, Tooke-Miller C, Varner M, et al. Evaluation of a noninvasive transcranial Doppler and blood pressure-based method for the assessment of cerebral perfusion pressure in pregnant women. *Hypertens Pregnancy* 2000;19:331–40.
- van Veen TR, Panerai RB, Haeri S, Griffioen AC, Zeeman GG, Belfort MA. Cerebral autoregulation in normal pregnancy and preeclampsia. *Obstet Gynecol* 2013;122:1064–9.
- ACOG Practice Bulletin no. 202: gestational hypertension and preeclampsia. *Obstet Gynecol* 2019;133:1.
- Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- Panerai RB, White RP, Markus HS, Evans DH. Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. *Stroke* 1998;29:2341–6.
- Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB; International Cerebral Autoregulation Research Network (CARNet). Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab* 2016;36:665–80.
- Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;26:1014–9.
- Panerai RB, Kerins V, Fan L, Yeoman PM, Hope T, Evans DH. Association between dynamic cerebral autoregulation and mortality in severe head injury. *Br J Neurosurg* 2004;18:471–9.
- Oehm E, Hetzel A, Els T, et al. Cerebral hemodynamics and autoregulation in reversible posterior leukoencephalopathy syndrome caused by pre-/eclampsia. *Cerebrovasc Dis* 2006;22:204–8.
- Intharakham K, Beishon L, Panerai RB, Haunton VJ, Robinson TG. Assessment of cerebral autoregulation in stroke: a systematic review and meta-analysis of studies at rest. *J Cereb Blood Flow Metab* 2019;39:2105–16.
- Belfort MA, Grunewald C, Saade GR, Varner M, Nisell H. Preeclampsia may cause both overperfusion and underperfusion of the brain: a cerebral perfusion based model. *Acta Obstet Gynecol Scand* 1999;78:586–91.
- Belfort MA, Saade GR, Grunewald C, et al. Association of cerebral perfusion pressure with headache in women with pre-eclampsia. *Br J Obstet Gynaecol* 1999;106:814–21.
- Tolcher MC, Fox KA, Sangi-Haghpeykar H, Clark SL, Belfort MA. Intravenous labetalol versus oral nifedipine for acute hypertension in pregnancy: effects on cerebral perfusion pressure. *Am J Obstet Gynecol* 2020;223:441.e1–8.
- Johnson AC, Tremble SM, Chan SL, et al. Magnesium sulfate treatment reverses seizure susceptibility and decreases neuroinflammation in a rat model of severe preeclampsia. *PLoS One* 2014;9:e113670.
- Belfort M, Allred J, Dildy G. Magnesium sulfate decreases cerebral perfusion pressure in preeclampsia. *Hypertens Pregnancy* 2008;27:315–27.
- Nogueira RC, Lam MY, Llwyd O, et al. Cerebral autoregulation and response to intravenous thrombolysis for acute ischemic stroke. *Sci Rep* 2020;10:10554.
- Caldas JR, Panerai RB, Haunton VJ, et al. Cerebral blood flow autoregulation in ischemic heart failure. *Am J Physiol Regul Integr Comp Physiol* 2017;312:R108–13.
- Andersgaard AB, Herbst A, Johansen M, et al. Eclampsia in Scandinavia: incidence, substandard care, and potentially preventable cases. *Acta Obstet Gynecol Scand* 2006;85:929–36.

Author and article information

From the Department of Obstetrics and Gynecology, Stellenbosch University, Cape Town, South Africa (Drs Bergman and Cluver); Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden (Dr Bergman); Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Dr Bergman); Translational Obstetrics Group, Department of Obstetrics and Gynaecology, University of Melbourne, Victoria, Australia (Dr Cluver); Mercy Perinatal, Mercy Hospital for Women, Heidelberg, Victoria, Australia (Dr Cluver); Department of Anesthesiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Dr Carlberg); Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX (Drs Belfort and Tolcher); Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom (Dr Panerai); and Department of Obstetrics and Gynecology, University Medical Center Groningen, Groningen, the Netherlands (Dr van Veen).

Received Nov. 28, 2020; revised Jan. 31, 2021; accepted March 2, 2021.

The authors report no conflict of interest.

The study was supported by the Swedish Medical Society, Märta Lundqvist Foundation, Mercy Perinatal Foundation, and Preeclampsia Foundation. L.B. is supported by the Swedish Society for Medical Research and the Swedish Research Council. C.C. receives salary support from the Mercy Perinatal Foundation.

Corresponding author: Lina Bergman, MD, PhD. lina.bergman.2@gu.se

SUPPLEMENTAL TABLE

Transfer function analysis with gain, phase, and coherence among groups

Variable	Eclampsia	Preeclampsia with severe features	Preeclampsia without severe features	Normal pregnancy	P value
N	16	18	32	21	
Gain VLF	0.50 (0.31–0.61)	0.44 (0.26–0.68)	0.57 (0.40–0.66)	0.43 (0.28–0.62)	NS
Gain LF	0.49 (0.37–0.77)	0.51 (0.29–0.82)	0.83 (0.63–1.02)	0.93 (0.68–1.01)	<.001
Phase VLF (rad)	0.43 (0.22–0.94) ^a	0.62 (0.26–1.10)	1.10 (0.66–1.54)	0.80 (0.38–1.20)	<.05
Phase LF (rad)	0.41 (0.35–0.63)	0.37 (0.04–0.60)	0.62 (0.30–0.85)	0.72 (0.52–0.96)	<.001
Coherence VLF	0.43 (0.28–0.65)	0.29 (0.18–0.44)	0.29 (0.20–0.47)	0.27 (0.18–0.49)	NS
Coherence LF	0.36 (0.27–0.59)	0.35 (0.19–0.50)	0.40 (0.27–0.55)	0.50 (0.34–0.65)	NS

Data are presented as median (interquartile range). Kruskal-Wallis tests were used for global differences among groups. Mann-Whitney *U*-tests with Bonferroni correction were used for pairwise comparisons. LF ranges from 0.07 to 0.20 Hz, and VLF ranges from 0.02 to 0.07 Hz.

LF, low frequency; NS, not stated; VLF, very low frequency.

^a $P < .01$ for difference between eclampsia and preeclampsia without severe features.

Bergman et al. Depressed dynamic cerebral autoregulation in eclampsia. *Am J Obstet Gynecol* 2021.