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

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Conflicts of interest

The authors report no conflict of interest.

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CONDENSATION AND SHORT VERSION OF TITLE

Condensation:

Dynamic cerebral autoregulation was less effective and cerebral perfusion pressure increased in women with eclampsia compared to women with preeclampsia and normotensive pregnancies.

Short title:

Depressed dynamic cerebral autoregulation in eclampsia

AJOG AT A GLANCE

Why was this study conducted?

To asses whether depressed dynamic cerebral autoregulation may be a part of the pathophysiological pathway to cerebral edema and eclampsia.

What are the key findings?

Women with pregnancies complicated by eclampsia demonstrate the least effective autoregulation followed by women with preeclampsia with severe features and then women with preeclampsia without severe features.

What does this study add to what is already known?

While there are studies demonstrating depressed dynamic cerebral autoregulation in preeclampsia when compared with normotensive controls, it is not known whether depressed dynamic cerebral autoregulation is associated with cerebral complications in preeclampsia. This study shows that depressed dynamic cerebral autoregulation may be an important pathophysiological mechanism in the pathophysiology of cerebral edema and eclampsia in pregnancies complicated by preeclampsia.

Keywords:

Preeclampsia, cerebral blood flow, cerebral autoregulation, cerebral perfusion pressure

ABSTRACT

Background

Dynamic cerebral autoregulation and cerebral perfusion pressure are altered in preeclampsia compared to normotensive pregnancy, but the connections between dynamic cerebral autoregulation, cerebral perfusion pressure and cerebral complications in preeclampsia remain unclear.

Objectives

To assess dynamic cerebral autoregulation and cerebral perfusion pressure after delivery in women with eclampsia, preeclampsia both with and without severe features, and in normotensive women.

Study design

Prospective case control study at a large referral hospital in Cape Town, South Africa. Women were included at diagnosis (cases) or at admission for delivery (controls). Transcranial Doppler examinations with continuous non-invasive blood pressure measurements and end-tidal CO_2 were conducted for cases and controls after delivery. Cerebral perfusion pressure and dynamic cerebral autoregulation index were calculated and values were compared between 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 women with eclampsia; (autoregulation index 3.9; interquartile range 3.1-5.2) compared to all other groups (preeclampsia with severe features, autoregulation index 5.6; interquartile range 4.4-6.8, preeclampsia without severe features, autoregulation index 6.8; interquartile range 5.1-7.4 and normotensive controls, autoregulation index 7.1; IQR 6.1-7.9). Women with eclampsia had

increased cerebral perfusion pressure (109.5 mm Hg; IQR 91.2-130.9) compared to women with preeclampsia without severe features and normotensive pregnancy (84 mm Hg; interquartile range 73.0-122.0 and 80.0 mm Hg; interquartile range 67.5-92.0, respectively), while there was no difference in cerebral perfusion pressure between women with eclampsia and 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).

Conclusions

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

INTRODUCTION

Preeclampsia, defined as hypertension with end-organ dysfunction after 20 weeks of gestation, is a multisystem disorder that complicates 4-6% 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 neurological effects of preeclampsia and its complications include an increased risk for white matter lesions, stroke, seizure disorders and vascular dementia later in life.[4-6]

The underlying pathophysiological mechanism of cerebral complications in preeclampsia has not been fully elucidated. Endothelial dysfunction at the blood-brain barrier level, in combination with-, or resulting in cerebral blood flow alteration, is a leading theory.[7] Studies using transcranial Doppler ultrasound have consistently shown increased cerebral perfusion pressure (CPP) in preeclampsia, albeit 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 under-perfusion injury and subsequent cerebral edema. Using transcranial Doppler and continuous BP measurement, DCA has been shown to be depressed in preeclampsia compared to normotensive pregnancy.[11] It is not known whether CPP and / or DCA have a direct role in the development of the cerebral complications of preeclampsia including cerebral edema and eclamptic convulsions, and whether CPP and / or DCA differ with regard to severity of disease.

We aimed to assess whether women with eclampsia demonstrate a less effective dynamic cerebral autoregulation, and have different cerebral perfusion pressure, than women with other phenotypes of preeclampsia (preeclampsia with and without severe features excluding eclampsia) and women with normotensive pregnancy.

MATERIALS AND METHODS

Ethical approval was obtained (protocol number N18/03/034, Federal Wide assurance number 00001372, Institutional Review Board number IRB0005239) and all included participants signed informed consent before being enrolled in the PROVE biobank.

Population

We included women with preeclampsia and women with normotensive pregnancy who were recruited to the PROVE (Preeclampsia Obstetric Adverse Events) biobank and database at Tygerberg Hospital, Cape Town, South Africa. The PROVE biobank is an ongoing collaborative project to facilitate research in the field of preeclampsia. Tygerberg Hospital is the largest referral hospital in the Western Cape Provence 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. PROVE biobank includes the majority of women with eclampsia and about 50 women with eclampsia are recruited yearly.

For this study, we included only women with singleton pregnancy. Exclusion criteria included known neurological or cardiac disease. For normotensive women, additional exclusion criteria were chronic hypertension and diabetes mellitus. All women were examined within five days of delivery, with the majority within 48 hours. Preeclampsia was defined according to the American College of Obstetricians and Gynecologists (ACOG) 2019 Practice Bulletin.[12] Eclampsia was confirmed when preeclampsia 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 Platelets (HELLP) syndrome and preeclampsia without severe features were diagnosed in accordance

with the ACOG Practice Bulletin.[12] A woman was considered normotensive if she had no documented systolic BP greater than or equal to 140 mmHg or a diastolic BP greater than or equal to 90 mmHg during her pregnancy.

Baseline data were obtained by interview and extraction from medical records. All data were entered and stored using REDCap (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 carried out postpartum in all women. At the time of transcranial Doppler (TCD) examination, non-invasive brachial systolic (SBP) and diastolic (DBP) blood pressure was measured. With the women in supine or semi-Fowlers position, maternal TCD interrogation of the middle cerebral artery (MCA) was carried out using a 2 MHz pulsed, range gated transcranial Doppler probe (Spencer Technologies, Seattle, WA), held in place using a head frame. 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 post facto calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal CO_2 ($EtCO_2$) was measured with 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 blood pressure were used when calculating the 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, $EtCO_2$ and heart rate were then calculated for each beat.[14] The reported CBFV and CPP values are 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 range (0.02–0.07 Hz), where dynamic CA is most active, as well as in low frequency range (0.07–0.20 Hz).[15]

The inverse FFT was then applied to estimate the impulse and step responses. The CBFV step response to a sudden change in BP was compared to 10 template curves proposed by Tiecks et al.[16] and the best-fit curve corresponded to the autoregulation index (ARI). A value of ARI=9 represents the best observed cerebral autoregulation, while 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]

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

Statistics

Demographic and clinical characteristics were presented as means with standard deviations (SD) and percentages and were compared between groups by ANOVA and chi-square tests. ARI, CPP and transfer function analyses (TFA) variables were presented as medians with interquartile range (IQR) and compared between 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 less than 0.05 was considered statistically significant. Data and statistical analyses were performed using SPSS version 26.0 (SPSS; PASW statistics) for MAC software package.

To detect a difference in ARI between women with preeclampsia and women with normotensive pregnancy, a sample size of 32 in each group was required based on 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 a 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 until 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 due to 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 inclusion in the control group (n=3). Of the 87 women included in the study, 16 had eclampsia, 18 had preeclampsia with severe features, 32 had preeclampsia without severe features and 21 had normotensive pregnancies.

Background characteristics

Maternal characteristics and pregnancy outcomes are presented in Table 1. Compared to 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 preeclampsia with severe features, 7 (39%) had HELLP, 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, pulmonary edema and renal impairment, respectively.

At time of transcranial Doppler examination, all women with eclampsia either had previous or current treatment with magnesium sulfate compared to 93% of women with preeclampsia with severe features and 76% of women with preeclampsia without severe features. Two (10%) of normotensive women had undergone treatment with magnesium sulfate for fetal neuroprotection due to threatened preterm labor. 94% of women with eclampsia or preeclampsia were on antihypertensive medications at the time of examination.

Dynamic cerebral autoregulation

ARI was measured either 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 left and right side 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 dynamic cerebral autoregulation, compared to all other groups (preeclampsia with severe features, ARI 5.6; IQR 4.4-6.8, preeclampsia without severe features, ARI 6.8; IQR 5.1-7.4 and normotensive controls, ARI 7.1; IQR 6.1-7.9). Pairwise comparisons between groups are presented in Figure 2a. Deterioration of cerebral autoregulation in the eclampsia group was confirmed by the reduced values of TFA phase shift for the VLF band (Supplemental Table 1).

There was no difference in ARI between women with preeclampsia with severe features, preeclampsia without severe features and normotensive controls after Bonferroni correction (Figure 2a). Similarly to the ARI, phase shift, gain and coherence were not different for these groups (Supplemental Table 1).

Cerebral perfusion pressure

The cerebral perfusion pressure (CPP) was also measured either 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 left and right side 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 to women with preeclampsia without severe features and normotensive controls (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 preeclampsia with severe features (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 between women with preeclampsia with severe features, preeclampsia without severe features and normotensive controls after Bonferroni correction (Figure 2b).

COMMENT

Principal findings

In this study, we found depressed DCA in women with eclampsia when compared to those with preeclampsia (both with and without severe features) and to normotensive controls. Women with eclampsia also demonstrated increased CPP, however, the difference was only present when compared to women with less severe disease and normotensive controls and did not hold true when compared with women with preeclampsia with severe features.

Results in context

It has previously been demonstrated that women with preeclampsia have depressed DCA compared to women with normotensive pregnancy.[11] In this study, we chose to use the same

method to calculate DCA and CPP in order to be able to compare our results and in addition, it is a safe method without discomfort for the study participant.[17] Our results complement this by showing that preeclampsia with evidence of neurological impairment (i.e. eclampsia) is associated with even less effective DCA, as shown by both ARI and the phase shift in the VLF range, than preeclampsia without neurological 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 preeclampsia with severe features. To our knowledge, only a single study on DCA in eclampsia has been published which described a severely reduced phase shift and elevated gain in two patients with eclampsia.[18] These changes are highly suggestive of depressed DCA in these patients.

While rarely applied in obstetric 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 stroke[19] and traumatic brain injury[17] show results in line with our study: significantly reduced ARI in patients with a stroke compared to controls[19] and a lower ARI in non-survivors versus survivors in traumatic brain injury, with ARI being an important variable able to reliably predict outcome.[19]

In our study, DCA was not different between women with preeclampsia and women with normotensive pregnancy which is in contrast to earlier findings.[11] This is most likely caused by a type 2 error associated with the four different groups which demands 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 preeclampsia (with and without severe features 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 postpartum whereas earlier studies have examined women before delivery. Since the 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 preeclampsia demonstrate an increased CPP compared to normotensive controls, but preeclampsia has also been associated with underperfusion (as indicated by CPP and compared to 95% confidence intervals for normal pregnancy): 52% of women with preeclampsia without severe features have underperfusion and 59% of women with preeclampsia with severe features 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 due to large variances and a small sample size. Other explanations could be treatment effects. Magnesium sulfate treatment has been shown to reduce the CPP in women with preeclampsia and increase the CPP at baseline.[17] In our population, the great majority of women with preeclampsia, and all women with eclampsia, had current or previous treatment with magnesium sulfate. Thus, this might have reduced the CPP in those groups and reduced the difference between women with preeclampsia and normotensive controls. The same decrease in CPP in preeclampsia 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 preeclampsia is neurological catastrophe. Therefore, it is imperative to understand the underlying pathophysiological pathways to cerebral complications in preeclampsia. 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 NMDA receptor, inhibition of neuroinflammation and perhaps unspecified effects on the blood brain barrier.[23] Magnesium sulfate has also been shown to decrease CPP in preeclampsia as discussed above.[24] If DCA and CPP are confirmed in future studies to be important in the development of cerebral complications in preeclampsia, medications such as magnesium sulfate, antihypertensive medications, and potential new drug targets could be evaluated with DCA and CPP endpoints. This could accelerate and facilitate identification of women at risk for cerebral complications, and thus decrease maternal morbidity and mortality.

In addition to the short-term complications, women with previous preeclampsia also suffer long-term neurological 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 preeclampsia and future studies should perhaps include a focus on cerebral blood flow regulation and long-term cerebrovascular health following a pregnancy complicated by preeclampsia.

In relation to other disorders, such as ischemic heart failure with high risk of later cognitive impairment and ischemic stroke, an ARI < 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 < 4. Thus, findings of later cognitive impairment in preeclampsia and eclampsia could perhaps have an association with ARI after diagnosis but this remains to be proven.

Research implications

The incidence of preeclampsia and eclampsia are affected by geographic, social and economic differences. This is the first study on DCA in this specific sub-Saharan population. The ARI

in both the control group and the group of women with preeclampsia appear to be higher than previously reported in different populations, though the women in our study were examined postpartum. 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 preeclampsia. To perform assessments on women with severe disease such as eclampsia is difficult in high income countries since the incidence is low (~1/2,000).[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 time period, the study remains underpowered to show differences between preeclampsia 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 onset of seizures in women with eclampsia. Thus, the depressed DCA might have evolved post seizures and might not have been present before, though this is unlikely given the progressive effect noted. To conduct measurements before onset of seizures would be impossible since eclampsia is unpredictable and rare, even in this population.

Conclusions

There is evidence of depressed DCA in eclampsia and our data suggest a clear "dose-response" effect, with the worst DCA in women with eclampsia and the best in normotensive women. In addition, women with eclampsia demonstrate increased CPP compared to women with preeclampsia without severe features and those with normotensive pregnancy.

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464 **Table 1.** Maternal characteristics and pregnancy outcomes of the study population.

	Eclampsia	**Preeclampsia with severe features**	**Preeclampsia without severe features**	**Normal pregnancy**
n	**16**	**18**	**32**	**21**
At baseline				
Maternal age (years)	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)
Metamphetamine use (%)	0 (0)	0 (0)	1 (3)	0 (0)
Missing (%)	1 (5)	0 (0)	0 (0)	2 (10)
Diabetes (%)			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)
Neurological 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 (weeks)	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 CS	0 (0)	1 (6)	2 (6)	14 (67)
Emergency CS	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	1 (6)	7 (39)	0 (0)	0 (0)
Pulmonary edema	1 (6)	9 (50)	0 (0)	0 (0)
*Renal impairment**	1 (6)	3 (17)	0 (0)	0 (0)
At TCD examination				
Mean arterial BP (mmHg)	103.6 (17.7)	103.4 (12.4)	108.7 (14.6)	88.9 (8.6)
Magnesium sulfate n (%)				
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)
Blood pressure 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)
$ETCO_2$ (mmHg)	33.6 (32.8,35,6)	34.3 (30.3,35.6)	34.8 (33.0,36.4)	33.6 (32.4,36,2)

Values are presented as means (standard deviation), medians (interquartile range) and numbers (percentage).
BMI; Body Mass Index, BP; blood pressure, GA; gestational age, Hb; Hemoglobin, HIV; Human Immunodeficiency Virus, SD; standard deviation
*Creatinine >120 μmol/L

Table 2. Cerebral perfusion pressure and autoregulatory index in the study population

	Eclampsia	Preeclampsia with severe features	Preeclampsia without severe features	Normal pregnancy	p-value
n	**16**	**18**	**32**	**21**	
CPP left (mm Hg)	105.0 (87-116.5)	96.6 (70.5-108.6)	89.3 (69.8-111.3)	76.0 (64.0-93.0)	<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)	<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)	<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)	<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)	<0.01
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)	<0.001
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	

Values are presented as medians with interquartile range. Kruskal Wallis for global differences between groups.
ARI; Autoregulatory Index, CPP; cerebral perfusion pressure

476 **Figure legends**
477
478 **Figure 1.** Flow chart of the study population.
479
480 **Figure 2**. Dot-plot of dynamic cerebral autoregulation index (ARI) (a) and cerebral perfusion
481 pressure (b) in eclampsia, preeclampsia with severe features (PE SF), preeclampsia without
482 severe features (PE whithout SF) and normotensive pregnancies. Medians are marked in each
483 group. Differences between groups are estimated by Mann Whitney U-test with Bonferroni
484 correction.

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