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Cerebral infarcts, edema, hypoperfusion and vasospasm in preeclampsia and eclampsia

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Conflicts of interest

The authors report no conflict of interest.

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TWEETABLE STATEMENT

Preeclampsia and in particular eclampsia are associated with cerebral infarcts, cerebral edema, decreased cerebral perfusion and vasospasm.

SHORT TITLE

Pathophysiology of eclampsia

AJOG AT A GLANCE

Why was this study conducted?

Eclampsia has previously been associated with infarctions on conventional magnetic resonance imaging (MRI). This needs verification in larger prospective studies. Advanced MRI techniques including cerebral diffusion (shows subclinical edema), perfusion (capillary blood flow) and angiography can increase the understanding of underlying pathophysiology of eclampsia.

What are the key findings?

Eclampsia was associated with cerebral infarcts, increased diffusion, hypoperfusion and vasospasm.

What does this study add to what is already known?

Our data provide evidence against hyperperfusion of cerebral arteries, previously thought to cause cerebral edema in eclampsia. Rather, women with eclampsia seem to suffer from insufficient cerebral perfusion. This is important knowledge to guide future interventions for neuroprotection. In addition, we provide robust evidence of presence of cerebral infarcts, causing potential irreversible injury after eclampsia.

ABSTRACT

Background

Eclampsia, a serious pregnancy complication, is associated with cerebral edema and infarctions but the underlying pathophysiology remains largely unexplored.

Objectives

To assess the pathophysiology of eclampsia using specialized magnetic resonance imaging that measures diffusion, perfusion, and vasospasm.

Study design

This was a cross-sectional study recruiting consecutive pregnant women between April 2018 to November 2021 at Tygerberg Hospital, Cape Town, South Africa. We recruited women with eclampsia, preeclampsia, and normotensive pregnancies who underwent magnetic resonance imaging after birth. Main outcome measures were cerebral infarcts, edema, and perfusion using intravoxel incoherent motion imaging and vasospasm using magnetic resonance imaging angiography. The imaging protocol was established before inclusion.

Results

Forty-nine women with eclampsia, 20 with preeclampsia and 10 normotensive women were included. Cerebral infarcts were identified in 34% of eclamptic, 5% of preeclamptic (risk difference (RD) 0.29; 95% confidence interval (CI) 0.06 to 0.52, p=0.012) and in no normotensive controls. Eclamptic women were more likely to have vasogenic cerebral edema compared to preeclamptic (80% *vs* 20%, RD 0.60; CI 0.34 to 0.85, p<.001) and normotensive women (RD 0.80; CI 0.47 to 1.00, p<.001). Diffusion was increased in eclampsia in the parietooccipital white matter (mean difference (MD) 0.02 $x10^{-3}$ mm^2/s, CI 0.00 to 0.05, p=0.045) and the caudate nucleus (MD 0.02 $x10^{-3}$ mm^2/s, CI 0.00 to 0.04, p=0.033) when compared to preeclamptic women. Diffusion was also increased in eclamptic women in the frontal (MD 0.07 $x10^{-3}$ mm^2/s, CI 0.02 to 0.12, p=0.012) and parietooccipital white matter

(MD 0.05 x10^{-3} mm^2/s, CI 0.02 to 0.07, p=0.03) and the caudate nucleus (MD 0.04 x10^{-3} mm^2/s, CI 0.00 to 0.07, p=0.028) when compared to normotensive women. Perfusion was decreased in edematous regions. Hypoperfusion was present in the caudate nucleus in eclampsia (MD -0.17 x10^{-3} mm^2/s, CI -0.27 to -0.06, p=0.003) when compared to preeclampsia. There were no signs of hyperperfusion. Vasospasm was present in 18% of eclamptic, 6% of preeclamptic and none of the controls.

Conclusions

Eclampsia is associated with cerebral infarcts, vasogenic cerebral edema, vasospasm and decreased perfusion, all not usually evident on standard clinical imaging. This may explain why some have cerebral symptoms and signs despite having normal conventional imaging.

Keywords

Eclampsia, preeclampsia, pathophysiology, hypoperfusion, vasospasm, hyperperfusion

INTRODUCTION

Preeclampsia, a life-threatening complication of pregnancy, occurs when a woman develops hypertension with end-organ injury in the second half of pregnancy.[1] One of the most feared complications of preeclampsia is eclampsia. Eclampsia presents with generalized tonic-clonic seizures and is associated with cerebral edema in 71-80% of cases.[2-4] The etiology is largely unknown and there is no directed treatment.

Cerebral edema can be visualized on both computerized tomography scan and conventional magnetic resonance imaging (MRI). It is defined as an increase in brain water content. Common etiologies are cytotoxic (direct cell injury and swelling), vasogenic (blood brain barrier injury), osmotic (changes in osmolality in plasma or interstitium) or interstitial (increased ventricular pressure). Diffusion-weighted imaging (DWI), is a MRI technique based on differences in random Brownian motion of water molecules between different tissues. This permits separation of vasogenic from cytotoxic edema.

Advanced MRI techniques can be used to assess cerebral diffusion, perfusion and vessel vasospasm and could be used to further understand the etiology of edema. Intravoxel incoherent imaging (IVIM), is an advanced DWI technique, which enables the extraction of both water diffusion and capillary perfusion.[5] If cerebral water diffusion is raised, it indicates increased brain water content. Cerebral perfusion can be measured by utilizing the IVIM technique by visualizing blood microcirculation in capillary networks of cerebral tissue.[5-7] A decreased perfusion indicates insufficient blood flow to a region. To measure vasospasm, 3D Time-of-flight MR angiography is utilized.

Cerebral diffusion, perfusion and vasospasm have not been studied in preeclampsia and eclampsia. If affected, it may explain the occurrence of neurological signs and symptoms in women with preeclampsia and eclampsia who do not have evidence of pathology on conventional MRI. It could also offer important insights into the pathophysiology of eclampsia, directing future research.[8] We therefore used these advanced MRI techniques to study women with eclampsia, preeclampsia and normotensive controls.

MATERIALS AND METHODS

Study cohort

This cross-sectional prospective study, included women recruited to the Preeclampsia Obstetric Adverse Events (PROVE) biobank at Tygerberg Hospital, Cape Town, South Africa.[9] Tygerberg is the largest referral hospital in the Western Cape Province, with over 8,500 high-risk deliveries a year.[9]

Women were prospectively included after a diagnosis of eclampsia or preeclampsia or at admission for delivery for controls. MRI was performed postpartum before discharge after birth. We included women who did not have a clinical indication for imaging, such as a suspicion of stroke. Women with known neurological or cardiac disease were ineligible. For normotensive women, additional exclusion criteria included chronic hypertension and diabetes mellitus. Baseline data were obtained by interview and extraction from medical records. Women were followed up until discharge. Data were recorded on a Research Electronic Data Capture database[10] and double checked for accuracy.

Exposures

Preeclampsia was defined according to the American College of Obstetricians and Gynecologists Practice Bulletin but significant proteinuria was also required (protein creatinine ratio ≥ 30 mg/mmol (0.3 mg/mg) or ≥ 0.3g protein in a 24 hour urine collection or urine dipstick >1+ on more than one occasion).[11] We only included women with preeclampsia with severe features according to the same classification. This approach was used to distinguish eclampsia as an organ-specific complication to preeclampsia with other severe features.

Eclampsia was defined as generalized tonic-clonic seizures in a woman with preeclampsia in the absence of another etiology. We subdivided eclampsia into eclampsia only (one eclamptic seizure with no other neurological symptoms) or complex eclampsia (women who had multiple seizures, Glasgow Coma Scale < 13 or eclampsia together with other organ complications).

Pulmonary edema was diagnosed when there was worsening dyspnea, fine bibasal inspiratory crackles on auscultation and features of pulmonary edema on chest x-ray. Hemolysis, elevated liver enzymes and low platelets syndrome was defined as a platelet count < 100×10^9/L, aspartate aminotransferase > 70 U/L, and hemolysis (lactate dehydrogenase > 600 U/L or hemolysis on a peripheral blood smear). Renal impairment was defined as a serum creatinine >120 µmol/L which is higher than the ACOG definition. Severe hypertension was defined as a blood pressure ≥ 160 mm Hg systolic and/or a diastolic blood pressure ≥ 110 mm Hg.

Outcomes measures

MRI was performed at 1.5T (Aera, Siemens Healthcare, Erlangen, Germany). The protocol included sagittal 2DT1 weighted spin echo, axial 2DT2 weighted spin echo, axial 2DT2 weighted gradient echo, axial 2D fluid attenuated inversion recovery, and axial diffusion

weighted sequences. The DWI was acquired with nine b-values for separation of diffusion and perfusion parameters, using IVIM.[5] All assessors were blinded to clinical exposures. Of the outcomes in our study, only cerebral edema (vasogenic and cytotoxic) can be visualized on a conventional MRI protocol.

Acute cerebral infarcts were defined as high intensity lesions on the b_{1000} DWI with corresponding low intensity on the Apparent Diffusion Coefficient (ADC) maps. Vasogenic cerebral edema was defined as high intensity white matter lesions on Fluent Attenuated Inversion Recovery (FLAIR) and ADC images, and low signal on DWI. Edema volume was calculated by adding the areas of edema in individual slices, multiplied with slice thickness.

The IVIM parametric maps (D, D* and f) were calculated from multi b-value DWI sequence using commercially available software (Olea Sphere 3.0, Olea Medical, La Ciotat, France). These metrics correspond to the rate of water self-diffusion (D), which relates to tissue water content, pseudo-diffusion related to capillary blood flow velocity (D*), and volume fraction of perfused capillaries (f).[5] D, D* and f were measured in the frontal white matter, the parietooccipital white matter, the caudate nucleus, the lentiform nucleus, and the thalamus. Estimates were obtained from averages of the right and left sides in two or three slices. The same measurements were obtained from regions of edema, when present.
Cerebral diffusion was defined as the diffusion coefficient, and used as a sign of subclinical edema. Cerebral perfusion was assessed using pseudodiffusion and perfusion fraction, yielding the combined perfusion estimate, which correlates with the tissue capillary blood flow.[5]

Vasospasm was defined as a vessel segment with more than a 50% diameter reduction, as compared with adjacent normal appearing vessels and was evaluated on the 3D Time-of-flight MR angiography. The first and second segments of the anterior and posterior, and first segment of middle cerebral arteries were analyzed. As this assessment is subjective, independent evaluations were performed by both a radiologist and a neuroradiologist who were blinded to clinical data. Segments in which both readers detected more than 50% diameter reduction were assigned positive for vasospasm, not including hypoplastic segments of the first segments of the anterior and posterior cerebral arteries.

Further description of MRI sequences parameters can be found in **Supplemental Table 1**.

Statistical methods

Descriptive data are presented as means with standard deviations or medians with interquartile ranges for numeric variables, and as numbers with percentages for categorical variables. Binary variables were analyzed using the Farrington-Manning test for the risk difference between groups. Numeric variables were analyzed using Welch's T-test, accounting for unequal variances between groups. Results are presented as mean difference (MD) with 95% confidence intervals. Differences in diffusion and perfusion in edema regions vs parieto-occipital white matter were evaluated using paired T-test. Evaluations in subgroups with few observations ($n<6$) were performed using non-parametric permutation tests and corresponding confidence intervals were calculated by test inversion. Positively skewed variables were log-transformed prior to analysis and the fold-change between groups calculated by exponentiating the mean difference on log scale. All statistical tests were performed at the 5% significance level. Statistical analyses were performed using

SAS/STAT® Software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Sample size

Previous studies found a large variation in presence of cerebral infarcts on MRI.[2,3,12] We aimed for a sample size of 50 women with eclampsia, 20 with preeclampsia, and 10 normotensive controls to be able to detect a difference in cerebral ischemia between groups. This is similar to other larger prospective studies.[2,3]

Ethics approval and registration details

Ethics approval was obtained from Stellenbosch University Health Research Ethics Committee (protocol number N18/03/034, Federal Wide assurance number 00001372, Institutional Review Board number IRB0005239). All participants or their guardians signed informed consent. The biobank is registered (ISRCTN10623443) and the protocol is published.[9]

Data availability

Anonymized data is available on request after approval by the corresponding author.

RESULTS

Participants

Eighty-one women had MRI examinations between April 2018 and November 2021. The median (range) time from delivery to MRI was 3 (1–6) days for women with preeclampsia and 1 (0–13) days for women with eclampsia. Twelve (60%) women with preeclampsia and 10 (20%) women with eclampsia had MRI performed more than 48 hours after delivery. Two

women had clinically evident strokes and were excluded. Forty-nine women had eclampsia, 20 had preeclampsia without eclampsia and 10 had a normotensive pregnancy (**Figure 1**). During the study period, 101 women with eclampsia were included in the PROVE biobank. Most common reason for not performing an MRI was unavailability of the MRI. There were no major differences in background characteristics between women who underwent an MRI and those who did not (**Supplemental table 2**).

Maternal characteristics and pregnancy outcomes

Background data can be found in **Table 1**. Women with preeclampsia and eclampsia were more often nulliparous, less likely to have attended antenatal care and more likely to experience a stillbirth compared to normotensive pregnancies. Women who experienced eclampsia were also more likely to use alcohol and smoke cigarettes during pregnancy (**Table 1**). All women with preeclampsia and eclampsia were treated with antihypertensive medication. All women with preeclampsia had one or more severe features; seventeen women had severe hypertension, 11 women had pulmonary edema, six women experienced HELLP-syndrome and six women had renal impairment. One woman with preeclampsia only had headache as a severe feature. Chronic hypertension occurred in five (25%) of women with preeclampsia and two (4%) of women with eclampsia (**Table 1**).

Cerebral infarcts

Sixteen (34%) women in the eclampsia group had cerebral infarcts compared to one (5%) in the preeclampsia group (risk difference 0.29; 95% CI 0.06 to 0.52, p=0.012) and none (0%) in the normotensive group (risk difference 0.34; 95% CI 0.03 to 0.65, p=0.030). (**Table 2**, **Figure 2)**

Vasogenic cerebral edema

In the eclampsia group, 39 (80%) had vasogenic cerebral edema on MRI compared with 4 (20%) in the preeclampsia (risk difference 0.60; 95% CI 0.34 to 0.85, p<.001) and none (0%) in the normotensive group (risk difference 0.80; 95% CI 0.47 to 1.00, p<.001) (**Table 2**, **Figure 2)**. When vasogenic cerebral edema was present, women with eclampsia had a larger volume of edema compared with women with preeclampsia, presented in **Figure 3** (fold change 12.2; 95% CI 3.51 to 42.7, p<.001).

Systemic blood pressure was not associated with cerebral edema (p=0.99 for severe hypertension and p=0.51 for chronic hypertension).

Diffusion (subclinical cerebral edema)

Women with eclampsia had increased diffusion in frontal white matter (MD 0.07 $x10^{-3}$ mm^2/s; 95% CI 0.02 to 0.12, p=0.012), the parietooccipital white matter (MD 0.05 $x10^{-3}$ mm^2/s; 95% CI 0.02 to 0.07, p=0.003) and the caudate nucleus (MD 0.04 $x10^{-3}$ mm^2/s; 95% CI 0.00 to 0.07, p=0.028) compared to women with normotensive pregnancies (**Table 3**). Women with preeclampsia had increased diffusion estimates in the frontal white matter (MD 0.07 $x10^{-3}$ mm^2/s; 95% CI 0.00 to 0.14, p=0.048), and a tendency for increased diffusion in both the parietooccipital white matter (MD 0.02 $x10^{-3}$ mm^2/s; 95% CI -0.01 to 0.05, p=0.12) and caudate nucleus regions (MD 0.02 $x10^{-3}$ mm^2/s; 95% CI -0.01 to 0.05, p=0.25) compared to women with normotensive pregnancies (**Table 3, Figure 4**).

Women with eclampsia had increased diffusion in parietooccipital white matter (MD 0.02 $x10^{-3}$ mm^2/s; 95% CI 0.00 to 0.05, p=0.045) and caudate nucleus regions (MD 0.02 $x10^{-3}$ mm^2/s; 95% CI 0.00 to 0.04, p=0.033) when compared to those with preeclampsia (**Table 3**).

Perfusion

Women with eclampsia had decreased perfusion in the caudate nucleus compared to women with preeclampsia (mean difference -0.17 $x10^{-3}$ mm^2/s, 95% CI -0.27 to -0.06, p=0.003) (**Table 3, Figure 4**). There were no significant differences between women who had experienced eclampsia and normotensive controls.

Vasospasm

Vasospasm was present in eight (18%) with eclampsia compared to one (5.6%) with preeclampsia (risk difference 0.13; 95% CI -0.07 to 0.32, p=0.20) and none (0%) in the normotensive group (risk difference 0.18; 95% CI -0.06 to 0.43, p=0.14) (**Table 2, Figure 4**).

Diffusion and perfusion in women with cerebral edema

In women with cerebral edema visible on conventional MRI, we compared women with eclampsia to preeclampsia. There was a tendency for lower perfusion in the eclampsia group when compared to those with preeclampsia (fold change 0.57, 95% CI 0.26 to 1.33, p=0.19) (**Table 4**). When comparing edema regions to normal appearing parieto-occipital white matter, there was an increase in water diffusion (MD 0.68 mm^2/s $x10^{-3}$; 95% CI 0.59 to 0.76, p<.001) and reduction of perfusion (MD -1.00 mm^2/s $x10^{-3}$; 95% CI -1.09 to -0.91, p<.001) in edema regions (**Table 5**).

MRI findings in women with complex eclampsia

Women with only one eclamptic seizure and no other end-organ involvement were compared to women with complex eclampsia (multiple seizures and/or additional neurological symptoms and/or other organ complications). There were no significant differences in the prevalence of cerebral infarcts (6/20 [30%] *vs* 10/29 [37%], p=0.61) or vasogenic cerebral

edema (15/20 [75%] *vs* 24/29 [83%], p=0.51) between the groups. Also, there were no differences in the prevalence of vasospasm (4/29 [15%] *vs* 4/20 [22%], p=0.56).

There were no differences in diffusion or perfusion when women with complex eclampsia were compared to women with eclampsia without additional complications (**Supplemental Table 3**).

COMMENT

Principal findings

Cerebral infarcts and edema are common in women who experienced eclampsia. Increased diffusion (subclinical edema) was observed in several regions in eclamptic women compared to normotensive women and women with preeclampsia. Hyperperfusion was not identified in eclampsia and preeclampsia. In contrast, certain areas showed decreased cerebral capillary blood flow, especially when associated with cerebral edema. Vasospasm was present in one in five women with eclampsia.

Preeclampsia with severe features does not have similar pathology as eclampsia and cerebral infarcts and vasospasm is uncommon. Approximately one of five women with severe preeclampsia have cerebral edema.

Results in context of what is known

Previously, it was thought that eclampsia was reversible and not associated with long term complications. We, and others have now shown that cerebral infarcts are common in eclampsia which might be potentially irreversible.[2,3,12] Interestingly, women who experience only one seizure without other end-organ involvement have a similar risk of cerebral infarcts to those who have experienced multiple seizures or eclampsia with other end-organ

involvement. Imaging and ongoing neurological follow up may be warranted for all who have experienced eclampsia.

Cerebral edema is common in eclampsia, affecting 80% of women in this cohort. Cerebral diffusion (subclinical cerebral edema) was also increased in women with eclampsia, likely reflecting an increase in microscopic tissue water content in this group. Our study is the first to evaluate diffusion in eclampsia and this could be important for understanding the pathophysiology of eclampsia.

Our data show that eclampsia is associated with hypoperfusion and not hyperperfusion, particularly in areas with cerebral edema. It is therefore unlikely that forced cerebral capillary vessel dilatation and hyperperfusion play a role in the development of eclampsia. Notably, the caudate nucleus is particularly affected by hypoperfusion in this South African cohort. This is in accordance with our previous results showing hypoperfusion of the caudate nucleus in preeclampsia compared to normotensive controls in a Swedish cohort.[13]

Vasospasm has been studied in some older case-reports or series of women with eclampsia and preeclampsia.[14-16] In some, vasospasm was found in several women with eclampsia and preeclampsia and resolved with resolution of cerebral edema. In others, vasospasm was not present.[17,18] These discrepancies may be due to differences in imaging technique and criteria for vasospasm and timing of imaging, as this is likely a dynamic process. Our results, from the largest prospectively included cohort of women with eclampsia and preeclampsia, support the presence of vasospasm in eclampsia.

Research implications

Women with eclampsia who have cerebral infarcts may have an even higher risk of developing longer term neurological sequelae than women without infarcts and should be followed up in future research.

If cerebral perfusion is decreased in eclampsia, it is important to evaluate the effects of antihypertensive and neuroprotective treatments on cerebral blood flow. The effect of acute decreases in systemic blood pressure on cerebral autoregulation and subsequent perfusion has not been studied.

Clinical implications

Conventional imaging does not rule out cerebral pathology in women who have experienced eclampsia and preeclampsia.

Women who have experienced preeclampsia and eclampsia may have an increased risk of neurological long-term sequelae such as epilepsy, cognitive decline, and dementia in this population irrespective of normal conventional imaging.[19-21] Long term follow up and education about the potential consequences of eclampsia may be needed.

Women presenting with neurological signs and symptoms who undergo a normal conventional MRI brain imaging may still have pre-clinical brain edema and perfusion defects.

Strengths and Limitations

This is the first study of women with eclampsia undergoing MRI imaging using a protocol to assess diffusion, perfusion and vasospasm. We present novel findings of pre-clinical edema, perfusion deficits and vasospasm in eclampsia and preeclampsia. MRI examinations were performed in women who did not qualify for clinically indicated imaging in our setting.

Women with is a suspicion of stroke were not included. The study was prospectively conducted, and MRI sequences were interpreted by blinded neuroradiologists.

The study has limitations. All imaging was performed after the onset of complications. It is therefore not possible to draw conclusions around factors present before the development of eclampsia. For the perfusion estimates, lack of differences between groups could be due to the relatively low magnetic field and use of the IVIM technique for perfusion estimates, thereby decreasing the signal-to-noise ratio. However, an important advantage is that IVIM does not require contrast agent administration, which is why we chose to use it in this study. This allowed for antepartum measurements if needed and also allowed imaging in cases of where renal lesions where contrast agent administration for research would be ethically questioned. Thus, repeating the MRI investigation with higher field strength and/or contrast agent based perfusion measurements could be of value.

Ideally, we would want to image women before an eclamptic seizure to evaluate whether edema is present and precedes eclampsia. This is extremely challenging as eclampsia is unpredictable and MRI examinations are expensive and not readily available, particularly in settings where eclampsia is common.

Conclusions

Cerebral infarcts were present in one third of women who experienced eclampsia, independent of disease severity. Women with preeclampsia and in particular eclampsia have pre-clinical cerebral edema (increased diffusion). This may explain neurological signs and symptoms in these women when there is no clinically evident cerebral edema on conventional MRI. Hyperperfusion with forced capillary dilatation does not seem to be the underlying cause of edema in eclampsia. Vasospasm with decreased capillary blood flow (hypoperfusion) is more likely to contribute to cerebral edema formation and subsequent neuroinflammation in

preeclampsia and eclampsia. A conventional MRI does not rule out pathology in preeclampsia and eclampsia.

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504

505 **Table 1**. Baseline characteristics of the study cohort.

	Normotensive (n=10)	Preeclampsia* (n=20)	Eclampsia (n=49)
Demographics and baseline characteristics			
Age (years), mean (SD)	29.5 (6.1)	28.7 (7.7)	22.4 (5.6)
Body mass index (kg/m^2), mean (SD)**	30.0 (6.9)	28.2 (7.6)	24.8 (5.6)
Nulliparous	2 (20%)	8 (40%)	36 (74%)
Any antenatal care	9 (90%)	18 (90%)	41 (84%)
HIV positive	1 (10%)	3 (15%)	6 (12%)
Smoking during pregnancy	2 (20%)	2 (10%)	9 (18%)
Alcohol use during pregnancy	0 (0%)	0 (0%)	7 (14%)
Diabetes mellitus	0 (0%)	0 (0%)	0 (0%)
Chronic hypertension	0 (0%)	5 (26%)	2 (4%)
Mode of birth: vaginal elective or non-urgent CS emergency CS	1 (10%) 6 (60%) 3 (30%)	6 (30%) 2 (10%) 12 (60%)	17 (35%) 1 (2%) 31 (63%)
Gestation at delivery (weeks and days), median (range)	38+6 (27+3–41+3)	32+6 (21+2–36+1)	34+4 (24+2–40+5)
Antihypertensive medication at time of birth	0 (0)	20 (100%)	49 (100%)
Liveborn infant	9 (90%)	14 (70%)	41 (84%)
Birthweight (g), mean (SD)	2729 (842)	1559 (584)	2076 (946)
Maternal complications			
Maternal death	0 (0%)	0 (0%)	0 (0%)
Intensive care unit admission	0 (0%)	1 (5%)	4 (8%)
Eclampsia	0 (0%)	0 (0%)	49 (100%)
Recurrent eclampsia	0 (0%)	0 (0%)	17 (35%)
Intracranial hemorrhage	0 (0%)	0 (0%)	1 (2%)
Glasgow Coma Scale < 13	0 (0%)	0 (0%)	12 (24%)
Cortical blindness	0 (0%)	2 (10%)	2 (4%)
Pulmonary edema	0 (0%)	11 (55%)	1 (2%)
Inotropic support	0 (0%)	1 (5%)	1 (2%)
Renal impairment	0 (0%)	6 (30%)	10 (20%)
Dialysis	0 (0%)	1 (5%)	1 (2%)
HELLP syndrome	0 (0%)	6 (30%)	14 (29%)
Disseminated Intravascular Coagulation (INR >1.2)	0 (0%)	1 (5%)	5 (10%)

Severe hypertension	0 (0%)	17 (85%)	17 (35%)
Sepsis	0 (0%)	3 (15%)	4 (8%)
Venous thromboembolism	0 (0%)	0 (0%)	1 (2%)
Placental abruption	1 (10%)	2 (10%)	3 (6%)

Data are presented as mean (SD) or median (range) for numeric variables, and as numbers and percentages for categorical variables.

*All women had preeclampsia with severe features

**Data on body mass index is missing for 2 (20%) women in the control group, 8 (40%) of women with preeclampsia, and 24 (49%) of women with eclampsia.

Abbreviations: CS, caesarean section; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, low platelets; HIV, human immunodeficiency virus; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation.

506

507 **Table 2**. Vasogenic cerebral edema, infarcts and vasospasm in normotensive women

508 (controls) and in women with preeclampsia or eclampsia.

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Variable	Normotensive (n=10)	Preeclampsia (n=20)	Eclampsia (n=49)	Risk difference (95% CI)		
				Eclampsia vs Preeclampsia	Eclampsia vs Normotensive	Preeclampsia vs Normotensive
Cerebral infarcts	0 (0%)	1 (5.0%)	16 (34%)	0.29 (0.06 to 0.52) p=0.012	0.34 (0.03 to 0.65) p=0.030	0.05 (-0.09 to 0.19) p=0.47
Vasogenic cerebral edema	0 (0%)	4 (20%)	39 (80%)	0.60 (0.34 to 0.85) p<.001	0.80 (0.47 to 1.00) p<.001	0.20 (-0.06 to 0.46) p=0.13
Vasospasm*	0 (0%)	1 (5.6%)	8 (18%)	0.13 (-0.07 to 0.32) p=0.20	0.18 (-0.06 to 0.43) p=0.14	0.06 (-0.09 to 0.20) p=0.45

Numbers (percentages) are presented.

Comparisons between groups were performed using the Farrington-Manning test for the risk difference.

*Data on vasospasm missing for n=2 women in the preeclampsia group and n=5 women in the eclampsia group.

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511 **Table 3.** Diffusion and perfusion in normotensive women and in women with preeclampsia or eclampsia.

Variable	Normotensive (n=10)	Preeclampsia (n=20)	Eclampsia (n=49)	Mean difference (95% CI)		
				Eclampsia vs Normotensive	Preeclampsia vs Normotensive	Eclampsia vs Preeclampsia
Diffusion (D, mm^2/s x10^{-3})						
Frontal white matter	0.70 (0.06)	0.77 (0.11)	0.77 (0.08)	**0.07 (0.02 to 0.12) p=0.012**	**0.07 (0.00 to 0.14) p=0.048**	-0.00 (-0.06 to 0.06) p=0.95
Parietooccipital white matter	0.65 (0.03)	0.67 (0.03)	0.70 (0.06)	**0.05 (0.02 to 0.07) p=0.003**	0.02 (-0.01 to 0.05) p=0.12	**0.02 (0.00 to 0.05) p=0.045**
Caudate nucleus	0.67 (0.04)	0.68 (0.03)	0.70 (0.04)	**0.04 (0.00 to 0.07) p=0.028**	0.02 (-0.01 to 0.05) p=0.25	**0.02 (0.00 to 0.04) p=0.033**
Lentiform nucleus	0.67 (0.03)	0.68 (0.03)	0.69 (0.05)	0.02 (-0.01 to 0.04) p=0.15	0.01 (-0.01 to 0.04) p=0.34	0.01 (-0.01 to 0.03) p=0.47
Thalamus	0.65 (0.02)	0.67 (0.03)	0.67 (0.02)	0.02 (-0.00 to 0.03) p=0.093	0.01 (-0.01 to 0.03) p=0.33	0.01 (-0.01 to 0.02) p=0.51
Perfusion (fxD*, mm^2/s x10^{-3})						

Frontal white matter	1.42 (0.44)	1.19 (0.37)	1.23 (0.33)	-0.19 (-0.51 to 0.14) p=0.23	-0.22 (-0.57 to 0.12) p=0.19	0.04 (-0.17 to 0.24) p=0.73
Parietooccipital white matter	1.23 (0.14)	1.29 (0.17)	1.23 (0.16)	-0.00 (-0.11 to 0.10) p=0.96	0.06 (-0.06 to 0.18) p=0.33	-0.06 (-0.16 to 0.03) p=0.19
Caudate nucleus	1.11 (0.29)	1.32 (0.18)	1.15 (0.22)	0.04 (-0.18 to 0.25) p=0.72	0.20 (-0.02 to 0.42) p=0.067	**-0.17 (-0.27 to -0.06) p=0.003**
Lentiform nucleus	1.54 (0.35)	1.46 (0.21)	1.38 (0.21)	-0.16 (-0.42 to 0.10) p=0.19	-0.08 (-0.34 to 0.18) p=0.52	-0.08 (-0.20 to 0.04) p=0.18
Thalamus	1.34 (0.17)	1.42 (0.11)	1.38 (0.16)	0.03 (-0.09 to 0.16) p=0.59	0.07 (-0.05 to 0.20) p=0.23	-0.04 (-0.11 to 0.03) p=0.23

Data are presented as mean and standard deviation.

Comparisons between groups were performed using Welch's T-test, accounting for unequal variances between groups.

513 **Table 4.** Diffusion and perfusion in edema regions, in women with preeclampsia compared to

514 eclampsia.

Variable	Eclampsia (n=32)	Preeclampsia (n=3)	Fold change (95% CI)	p-value
Diffusion (D, mm^2/s $x10^{-3}$)	1.30 (1.2–1.6)	1.40 (1.2–1.4)	1.02 (0.81 to 1.26)	0.81
Perfusion (fxD*, mm^2/s $x10^{-3}$)	0.17 (0.1–0.3)	0.36 (0.3–0.4)	0.57 (0.26 to 1.33)	0.19

Data are presented as median and interquartile range.

Data were missing for one woman in the preeclampsia groups and seven women in the eclampsia group.

Comparison between groups were performed using non-parametric permutation test for the mean difference on log-transformed variables. Corresponding confidence intervals were calculated by test inversion.

Abbreviations: CI, confidence interval.

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518 **Table 5.** Diffusion and perfusion in edema regions versus parietooccipital white matter

519 without edema in 35 women with cerebral edema.

Variable	Edema regions	Parietooccipital white matter	Mean difference (95% CI)	p-value
Diffusion (D, mm^2/s $x10^{-3}$)	1.38 (0.24)	0.70 (0.05)	0.68 (0.59 to 0.76)	<.001
Perfusion (fxD*, mm^2/s $x10^{-3}$)	0.25 (0.18)	1.25 (0.17)	-1.00 (-1.09 to -0.91)	<.001

Descriptive data are presented as mean (SD).

Data to calculate diffusion and perfusion in edema regions missing for n=1 women with preeclampsia and n=7 women with eclampsia.

Statistical analyses were performed using paired T-test.

Abbreviations: CI, confidence interval; SD, standard deviation.

520

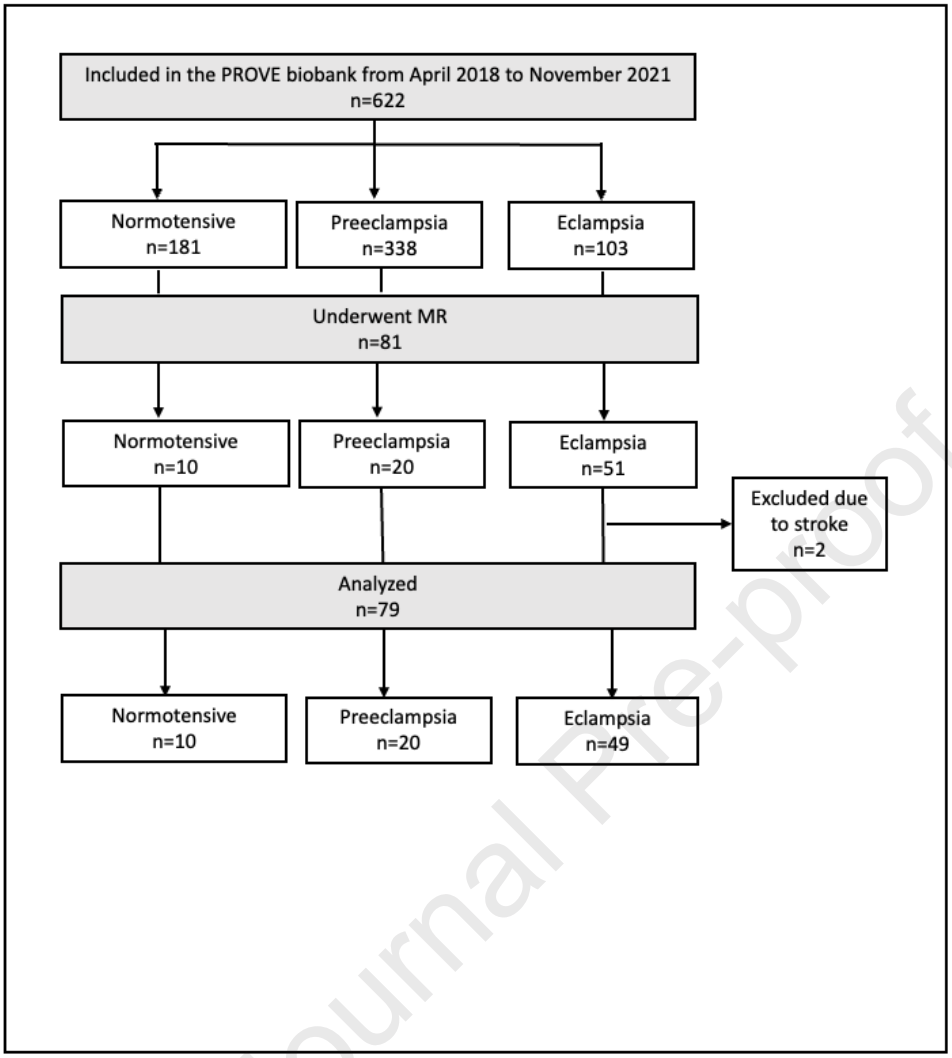
Figure legends

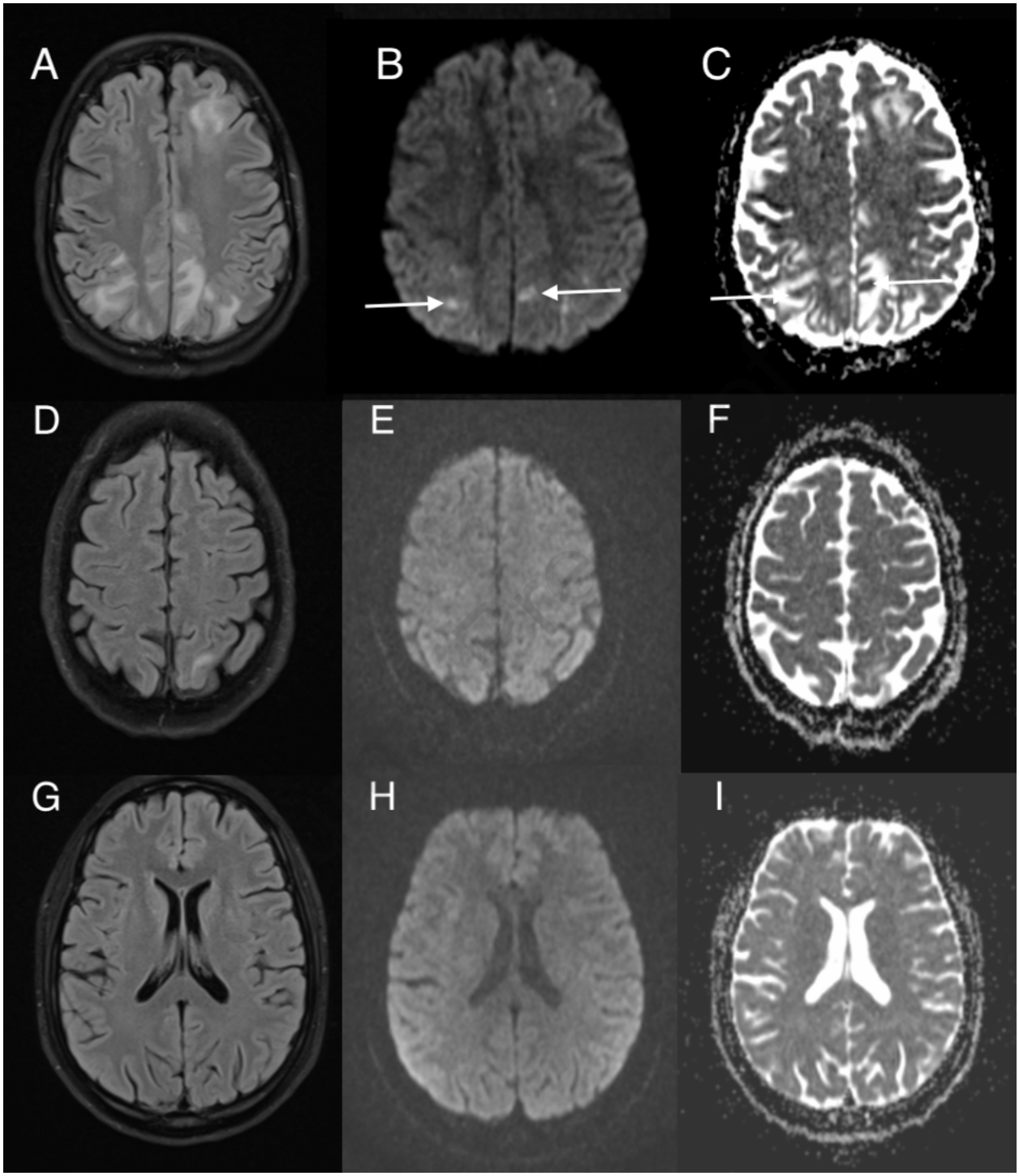
Figure 1. Flow chart of the study cohort, showing the number of women included in the biobank, who underwent MRI, and that had analyzed data.

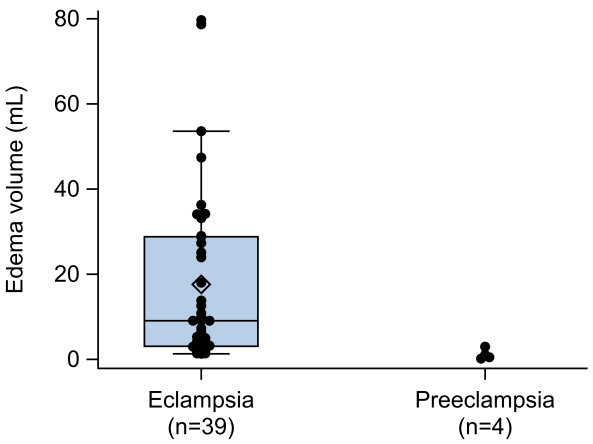
Figure 2. MRI demonstrating subcortical vasogenic cerebral edema in bilateral parietal lobes (a; FLAIR sequence), with scattered small areas of ischemia (arrows) (b; diffusion weighted sequence, c; ADC map) in a woman who experienced eclampsia. A smaller area of subcortical edema in a woman with preeclampsia (without eclampsia) is observed in the left parietal lobe (d; FLAIR image), without ischemic lesions (e; diffusion weighted sequence, f; ADC map). Corresponding FLAIR (g) and diffusion weighted image (h) and ADC map (i) from a normotensive control show normal findings.

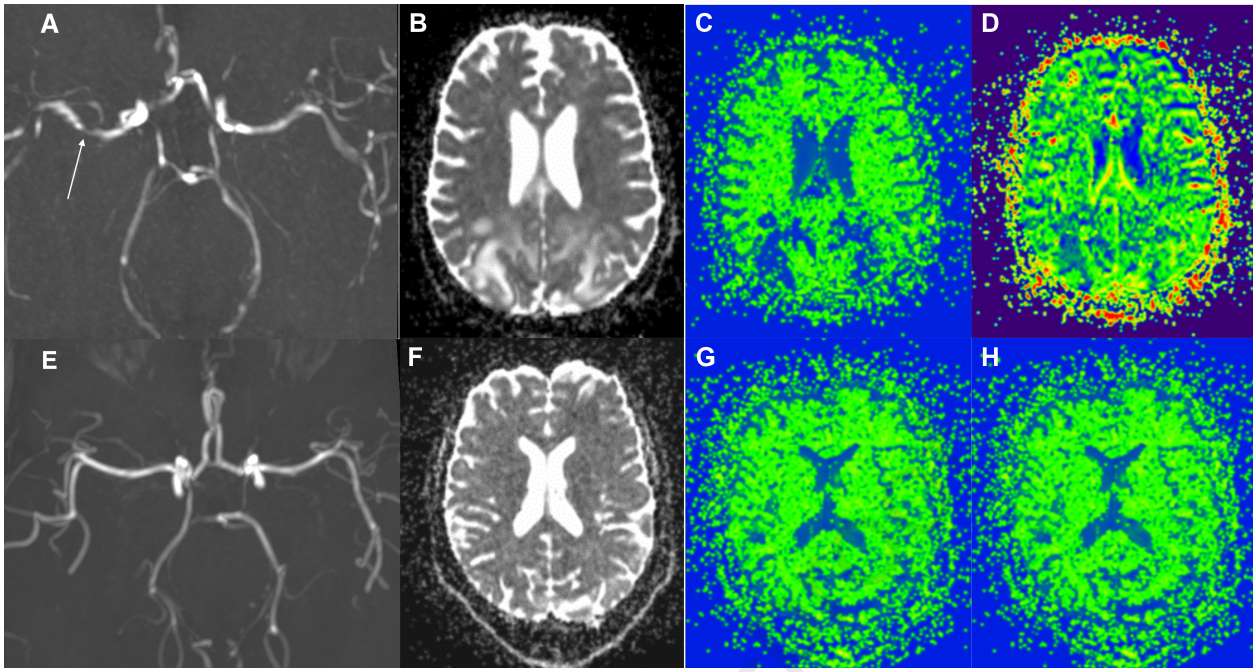
Figure 3. Box and scatter plot of edema volume in women with eclampsia and preeclampsia. Points are observed values. The box limits are the lower and upper quartiles. The line within the box represents the median and the diamond represents the mean. Box plot not shown in the preeclampsia group due to small sample size.

Figure 4. MRI images of cerebral arteries (a, e), diffusion (b, f) and perfusion (c,d, g,h) in a woman with eclampsia (a–d) and a normotensive control (e–h). MR images from a woman with eclampsia show vasospasm (arrow in a), increased water diffusion (D) (b) and low perfusion estimates (pseudodiffusion, D* in c, and perfusion fraction, f in d) in areas with edema.









Supplemental Table 1. MRI sequence parameters.

Sequence	Type	Orientation	Spatial resolution (mm)	TR (ms)/TE (ms)/flip angle (degree)	Number of excitations
T1 weighted	2D turbo spin echo	sagittal	0.6 x 0.6 x 4	389/9.7/150	3
T2 weighted	2D turbo spin echo	axial	0.6 x 0.6 x 4	5720/80/150	3
T2* weighted	2D gradient echo	axial	0.4 x 0.4 x 4	830/25/20	1
FLAIR	2D IR-spin echo	axial	0.7 x 0.7 x 4	8000/84/150	1
Diffusion weighted	2D echo planar imaging	axial	1.25 x 1.25 x 3	6500/119/90	1
MR angiography	3D time-of-flight	axial	0.4 x 0.4 x 0.5	27/7/25	1

MRI was performed on 1.5T (Aera, Siemens Healthcare, Erlangen, Germany). The examination protocol included sagittal 2DT1 weighted spin echo, axial 2DT2 spin echo, axial 2DT2 gradient echo, axial 2DFLAIR and axial diffusion weighted (DWI). The DWI sequence was acquired with nine b-values (0, 50, 100, 150, 200, 400, 600, 800, and 1000 s/mm^2 x 10^{-3}) for separation of diffusion and perfusion parameters.

Assessment of edema, ischemia, diffusion, and perfusion were performed by a blinded radiologist (DH). Vasogenic edema was evaluated on FLAIR images and quantified by manual outlining on individual slices. Edema volume was calculated as the sum of these areas multiplied by slice thickness.

The presence of ischemic lesions was assessed on the b_{1000} DWI images, where high signal intensity corresponding to cytotoxic edema was interpreted as a sign of acute ischemia.

The intravoxel incoherent imaging parametric maps (D, D* and f) were calculated from the multi b-value DWI sequence using commercially available software (Olea Sphere 3.0, Olea Medical, La Ciotat, France). These metrics correspond to the degree of water self-diffusion (D), pseudo-diffusion related to capillary blood flow (D*), and volume fraction of perfused capillaries (f) as described by Le Bihan.[9] D, D* and f were measured in the following regions: frontal white matter, parietooccipital white matter, caudate nucleus, lentiform nucleus, and thalamus. Estimates were obtained from averages of right and left sides in two or three slices.

Supplemental Table 2. Characteristics of women with eclampsia with and without MRI in the database.

Variable	With MRI (n=49)	Without MRI (n=52)
Demographics and baseline characteristics		
Age (years), mean (SD)	22.4 (5.6)	22.6 (6.3)
Body mass index (kg/m^2), mean (SD)	24.8 (5.6)	28.6 (7.6)
Nulliparous	36 (73.5%)	32 (61.5%)
Any antenatal care	41 (83.7%)	42 (80.4%)
HIV positive	6 (12.2%)	6 (11.5%)
Smoking during pregnancy	9 (18.4%)	4 (7.7%)
Alcohol use during pregnancy	7 (14.3%)	2 (3.8%)
Gestational diabetes mellitus	0 (0.0%)	1 (1.9%)
Chronic hypertension	2 (4.2%)	3 (5.8%)
Mode of birth		
Vaginal	17 (34.7%)	12 (23.1%)
Elective or non-urgent Cesarean section	1 (2.0%)	0 (0.0%)
Emergency Cesarean section	31 (63.3%)	39 (75.0%)
Gestation at delivery (weeks and days), median (range)	34+4 (24+2–40+5)	34+2 (23+0–41+6)
Liveborn infant	41 (83.7%)	42 (82.4%)
Birthweight (g), mean (SD)	2076 (946)	2125 (914)
Maternal complications		
Maternal death	0 (0.0%)	3 (5.8%)
Intensive care unit admission	4 (8.2%)	6 (11.5%)
Recurrent eclampsia	17 (34.7%)	17 (32.7%)
Glasgow Coma Scale <13	12 (24.5%)	9 (17.3%)
Cortical blindness	2 (4.1%)	3 (5.8%)
Pulmonary edema	1 (2.0%)	3 (5.8%)
Inotropic support	1 (2.0%)	2 (3.8%)
Renal impairment	10 (20.4%)	4 (7.7%)
Dialysis	1 (2.0%)	0 (0.0%)
HELLP syndrome	14 (28.6%)	10 (19.2%)
DIC INR >1.2	10 (20.4%)	1 (1.9%)
Severe hypertension	17 (34.7%)	20 (38.5%)
Sepsis	4 (8.2%)	5 (9.6%)
Venous thromboembolism	1 (2.0%)	1 (1.9%)
Placental abruption	3 (6.1%)	2 (3.8%)

Data are presented as mean (SD) or median (range) for numeric variables, and as number (percent) for categorical variables.
Abbreviations: DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, low platelets; HIV, human immunodeficiency virus; INR, international normalized ratio; SD, standard deviation.

Supplemental Table 3. MRI findings in women with eclampsia or eclampsia with complications.

Variable	Eclampsia with complications (n=29)	Eclampsia (n=20)	Mean difference (95% CI)	p-value
Diffusion (D, mm^2/s x10^{-3})				
Frontal white matter	0.78 (0.10)	0.76 (0.06)	0.02 (-0.03 to 0.07)	0.46
Parietooccipital white matter	0.70 (0.06)	0.70 (0.05)	0.01 (-0.03 to 0.04)	0.74
Caudate nucleus	0.71 (0.04)	0.69 (0.03)	0.02 (-0.01 to 0.04)	0.19
Lentiform nucleus	0.69 (0.06)	0.68 (0.04)	0.01 (-0.02 to 0.04)	0.36
Thalamus	0.67 (0.03)	0.67 (0.02)	-0.00 (-0.02 to 0.01)	0.68
Perfusion (fxD*, mm^2/s x10^{-3})				
Frontal white matter	1.21 (0.28)	1.25 (0.40)	-0.05 (-0.26 to 0.17)	0.67
Parietooccipital white matter	1.24 (0.16)	1.21 (0.18)	0.03 (-0.07 to 0.13)	0.56
Caudate nucleus	1.10 (0.24)	1.21 (0.19)	-0.11 (-0.24 to 0.02)	0.097
Lentiform nucleus	1.37 (0.20)	1.39 (0.23)	-0.03 (-0.16 to 0.10)	0.68
Thalamus	1.36 (0.19)	1.40 (0.11)	-0.04 (-0.13 to 0.05)	0.38

Data are presented as mean and standard deviation.
Statistical analyses were performed using Welch's T-test.