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ORIGINAL RESEARCH ARTICLE

Cognitive impairment in preeclampsia complicated by eclampsia and pulmonary edema after delivery

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Abstract

Introduction: We aimed to assess cognitive function in women with preeclampsia stratified by severity, before and after onset of disease.

Material and methods: Prospective study performed at a referral hospital in Cape Town, South Africa. Pregnant women between 20 and 42 weeks of gestation with eclampsia, pulmonary edema and preeclampsia without severe features, and a normotensive pregnancy were approached. Women were included at diagnosis of preeclampsia or at admission for delivery (women with normotensive pregnancies). Two cognitive assessments, the Cognitive Failure Questionnaire to assess the cognitive function subjectively before inclusion in the study, and Montreal Cognitive Assessment to assess the current cognitive function objectively before discharge from the hospital after delivery, were performed.

Results: We included 61 women with eclampsia, 28 with preeclampsia complicated by pulmonary edema, 38 with preeclampsia without severe features, and 26 with normotensive pregnancies. There was no difference in cognitive function from early pregnancy between groups. Women with eclampsia and preeclampsia complicated by pulmonary edema scored lower on the Montreal Cognitive Assessment at time of discharge compared with women with normotensive pregnancies. The results were attenuated in pulmonary edema after adjustment for confounders.

Conclusions: Women with preeclampsia complicated by pulmonary edema and in particular eclampsia had impaired cognitive function after onset of disease compared with women with normotensive pregnancies. The impairment did not seem to be present before onset of disease. Women with preeclampsia without severe features did not have impaired cognitive function.

KEYWORDS
cognitive function, eclampsia, preeclampsia, pulmonary edema

Abbreviations: ANOVA, analysis of variance; CFQ, Cognitive Failure Questionnaire; CI, confidence interval; HELLP, hemolysis, elevated liver enzymes and low platelets syndrome; MoCA, Montreal Cognitive Assessment; REDCap, Reserarch Electronic Data Capture.

1 | INTRODUCTION

Preeclampsia, defined as hypertension with end-organ dysfunction after 20 weeks of gestation, is a multisystem disorder that complicates about 4%-6% of all pregnancies.[1,2] Cerebral and cardiovascular complications, which include eclampsia and pulmonary edema, are some of the most severe outcomes and can result in maternal mortality and morbidity.[2] 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.[3-5] Women with previous preeclampsia have also reported a poorer quality of life and social functioning, and have an increased risk for post-traumatic stress disorder.[6,7]

The impact of preeclampsia and its complications on cognitive function is a field that requires further investigation. In 2018, a systematic review found that women with a history of preeclampsia reported subjective losses in cognitive function. They also noted that there were insufficient data to draw conclusions about the presence or absence of objective cognitive changes. This review excluded women with a history of eclampsia and assessed all women together irrespective of time after delivery.[8] Later in the same year, a large longitudinal cohort study found differences in raw neurocognitive scores when women with and without preeclampsia were compared decades after pregnancy. The differences were seen in the domains assessing psychomotor speed and executive function but not working memory, but after adjustment for possible confounders the associations were attenuated.[9]

Whether the impairment in cognitive function observed years after preeclampsia exists in closer proximity to the diagnosis of preeclampsia and its relation to severity of disease is uncertain. It is also not known whether women with preeclampsia have underlying cognitive function deficits before the diagnosis of preeclampsia. We therefore aimed to assess cognition subjectively, rating 6 months back, and objectively with testing performed at discharge after delivery.

Key message

Preeclampsia complicated by eclampsia or pulmonary edema demonstrated an acute impairment of cognitive function.

2 | MATERIAL AND METHODS

2.1 | Population

We included women with preeclampsia and normotensive pregnancies who were recruited to the PROVE biobank and database at Tygerberg Hospital, Cape Town, South Africa. Tygerberg Hospital is a referral hospital that manages only high-risk pregnancies and delivers over 7000 women a year. Tygerberg hospital provides medical care to women who do not have medical insurance. The PROVE biobank is an ongoing collaborative project that recruits women with preeclampsia and women with normotensive pregnancies to facilitate research in the field of preeclampsia and in particular preeclampsia with severe features, focusing on eclampsia and pulmonary edema. PROVE collects the recommended predictors and core-outcome sets recommended by CoLab to facilitate data sharing in preeclampsia research.[10]

For this study, we included women with singleton pregnancies who were able to speak and understand English, Xhosa or Afrikaans. Exclusion criteria included known neurological or cardiac disease. For normotensive women, additional exclusion criteria were chronic hypertension and diabetes mellitus. We included women with eclampsia, pulmonary edema (as an example of preeclampsia with severe features), preeclampsia without complications and normotensive pregnancies. Women with normotensive pregnancies were mainly recruited at time of admission to the hospital for a planned cesarean section.

Preeclampsia was defined according to the NICE guidelines.[11] Eclampsia was confirmed when preeclampsia was complicated by generalized tonic-clonic seizures in the absence of another etiology. Pulmonary edema was diagnosed when there was worsening dyspnea, fine bibasal inspiratory crackles on auscultation and features of pulmonary edema on chest X-ray. Women were considered to have preeclampsia without severe features if they did not meet the NICE guidelines classification of severe preeclampsia.[11] Fetal growth restriction may not have been diagnosed antenatally, as some women presented late with unsure gestational age. Pregnancies were considered to be normotensive if a woman consistently had a systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg during pregnancy. Hemolysis, elevated liver enzymes and low platelets syndrome (HELLP) was defined according to NICE guidelines[11] and renal impairment was defined as a serum creatinine >120 μmol/L.

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.[12] Data were double checked for accuracy and controlled with original data collection forms.

2.2 | Cognitive function testing

Cognitive function was assessed using two instruments: the Cognitive Failure Questionnaire (CFQ) and the Montreal Cognitive Assessment (MoCA) test. The CFQ is a subjective questionnaire that assesses the likelihood of committing errors in the completion of daily tasks such as the routines of everyday life.[13] The CFQ consists of 25 items that are scored on a 5-point scale (range: 0 [never] to 4 [very often]). Thus, the total score ranges from 0 to 100, with higher scores indicating more frequently occurring cognitive failures. Women included in this study were instructed to complete the items with specific reference to the past 6 months prior to admission to hospital in order to assess the cognitive function prior to onset

of preeclampsia. In the CFQ, there are four subscales that pertain to more specific areas of cognitive failures: memory (seven items, range: 0-28), distractibility (nine items, range: 0-36), blunders (seven items, range: 0-28), and names (two items, range: 0-8).[13]

The MoCA test is an objective assessment composed of a variety of cognitive domains assessing attention, concentration, executive function, memory, language, visuospatial abilities, abstract thinking, mathematical calculations and orientation.[14] The highest possible score is 30 points and a score of 26 points or greater indicates normal function in individuals with a total school education of more than 12 years. If total school education is <12 years, an additional point is added to the total score.[14]

The assessments were administered by trained research midwives and a trained medical student. All assessments were performed postpartum, as close to discharge as possible, to avoid situations where women could have been too tired or sick to perform adequately. The CFQ test was available in English and Afrikaans and questions were translated to Xhosa by an interpreter. The MoCA test was available in English and Afrikaans and performed in Xhosa if needed at time of assessment by the Xhosa-speaking research midwife. Translations to Xhosa from English for both the CFQ test and the MoCA test were checked for accuracy during the first five tests to ensure that the women understood the questions correctly and to secure validity.

2.3 | Statistical analyses

Demographic and clinical characteristics were presented as means with standard deviations (SD) and percentages and were compared between groups by analysis of variance (ANOVA) and Chi-square tests. MoCA and CFQ scores were presented as means with 95% confidence intervals (CI) and compared between groups using robust One-way ANOVA (parameter estimates with robust standard error to adjust for differences in variance) and pairwise comparisons with Bonferroni correction. To control for potential confounders, a robust multi-way ANOVA (parameter estimates with robust standard error to adjust for differences in variance) was conducted with maternal age, gestational age at birth, days from test to discharge and parity as continuous covariates and living conditions as a fixed effect, and were presented as estimated marginal means with 95% CI. Normotensive pregnancy was set as the reference group in pairwise comparisons. In all hypothesis tests, a P value <.05 was considered statistically significant. Data and statistical analyses were performed using SPSS version 26.0 (SPSS; PASW statistics) for MAC software package.

2.4 | Sample size

To our knowledge, CFQ has never previously been tested close to the time of diagnosis of preeclampsia. Previous publications have demonstrated a mean score for women with eclampsia of 44 with an SD of 16 and for women with previously normal pregnancy a mean of 36 with an SD between 11 and 14 when testing has been conducted years after pregnancy.[15,16] With an alpha value of 0.05 and power of 0.80, the sample size would be 25-60 in each group. For the MoCA test, there are, to the best of our knowledge, no publications in the field of preeclampsia.

2.5 | Ethical approval

The study had ethical approval (protocol number N18/03/034, Federal Wide assurance number 00001372, Institutional Review Board number IRB0005239) and all included participants signed an informed consent before being enrolled in the PROVE (Preeclampsia Obstetric Adverse Events) biobank. The study was initially approved on 28 February 2018 with annual progress reports approved yearly. Three women previously affected by severe preeclampsia were consulted about the cognitive function tests and time of testing. The study is registered with ISCRTN, registration number ISRCTN10623443.

3 | RESULTS

3.1 | Participants

This study was conducted from April 2018 until November 2019 during which time, 222 women were included into the PROVE biobank. Fifty-one women did not have cognitive function assessments as they were included in the biobank for other substudies. A total of 171 women had assessments for cognitive function. Eleven were excluded due to language barriers. Seven women from the group of preeclampsia without severe features were excluded as they developed renal impairment and/or HELLP. Of the 153 included in the study, 61 had eclampsia, 28 had preeclampsia complicated by pulmonary edema, 38 had preeclampsia without severe complications and 26 had normotensive pregnancies (Figure 1). The majority had both subjective (n = 140) and objective (n = 139) assessments performed. Both CFQ and MoCA tests were administered as close to discharge as possible and none of the participants was treated with magnesium sulfate at the time of testing.

3.2 | Background characteristics

Maternal characteristics and pregnancy outcomes are presented in Table 1. Women with eclampsia were generally younger, less often cohabitating, more often registered as students, more commonly nulliparous and more likely to smoke. Women with pulmonary edema were more commonly of black race, living in informal settlements, had shorter gestations and higher rates of termination of pregnancy before viability due to severe disease. Sixteen (26%) women with eclampsia and six (18%) women with pulmonary edema suffered from HELLP. Eleven (18%) of women with eclampsia and four (14%) of women with

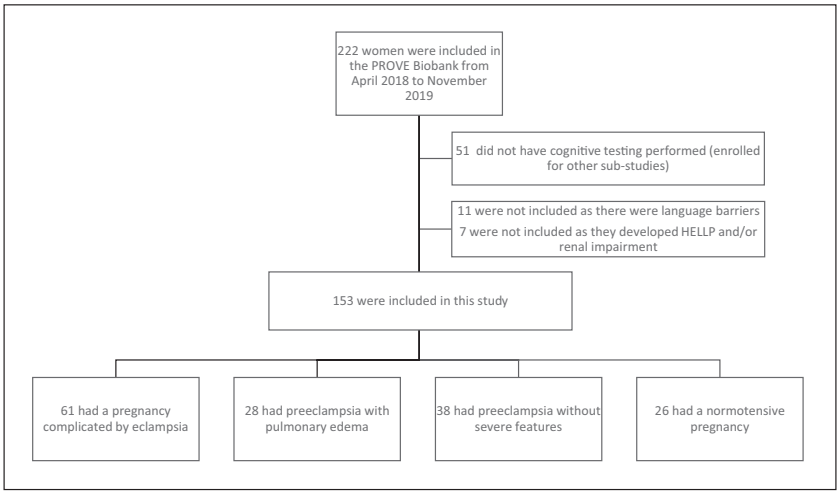

FIGURE 1 Flowchart describing the study population. HELLP, hemolysis, elevated liver enzymes, and a low platelet count syndrome

pulmonary edema developed renal impairment. None of the women had both eclampsia and pulmonary edema.

3.3 | CFQ assessment

There were no differences in the CFQ assessments between the groups before or after adjustment for potential confounders (Table 2). All groups scored similarly in the four subdomains of memory, distractibility, blunders and names (Table 3).

3.4 | MoCA assessment

MoCA scores were lower in women with eclampsia and pulmonary edema (21.6, 95% CI 20.4-22.7, $P < .001$ and 21.3, 95% CI 19.7-23.0, $P < .01$, respectively) when compared with normotensive women (25.8, 95% CI 24.1-27.4). When adjusted for confounders, results remained similar for women with eclampsia (21.7, 95% CI 20.5-22.9 vs 25.6, 95% CI 23.7-27.4, $P < .05$) (Table 2). For women with pulmonary edema, the results were attenuated after adjustments for confounders (21.8, 95% CI 20.0-23.5 vs 25.6, 95% CI 23.7-27.4, $P = .09$). In women with eclampsia and women with pulmonary edema, more than 75% had a score <26 (40/61 [76%] for pulmonary edema and 21/28 [81%] for eclampsia). In women with preeclampsia without severe features, 8/45 (18%) had a score <26 and in the normotensive group, 3/26 (12%) had a score <26. For the subdomains of the MoCA assessment, there was an overall difference in attention, language, abstraction, delayed recall and orientation but no difference in naming or visuospatial ability (Table 4).

4 | DISCUSSION

When women were asked to assess their cognitive function subjectively over the 6 months prior to delivery (corresponding to early pregnancy, before onset of disease), there were no differences in the overall or subdomain scores for any of the groups. At discharge, after delivery and thus after onset of disease, women with preeclampsia complicated by pulmonary edema or eclampsia demonstrated lower scores on the objective MoCA assessment for cognitive function when compared with normotensive women, but the difference was attenuated for women with pulmonary edema after adjustment for confounders. Women with preeclampsia without severe features showed no difference on MoCA scores when compared with normotensive women.

Previous studies have shown cognitive decline months to years after a pregnancy complicated by preeclampsia.[15-17] To our knowledge no studies have assessed cognitive function before delivery or assessed cognitive function objectively at time of disease. Our findings would imply that the cognitive decline observed postpartum in earlier studies does not exist before onset of disease and is reported only in preeclampsia with severe features after diagnosis. To support this theory, subjective cognitive decline seems to increase with severity of disease and in particular with the number of fits in women with previous eclampsia, arguing for a dose–response mechanism.[15] It would be important to follow up our findings with long-term studies to assess whether these acute findings found in our population are reversible and whether they correlate with longer term impaired cognitive function months to years after the pregnancy. In addition, cognitive function needs to be studied in combination with cerebral imaging and more in-depth cognitive function assessment in the short and long term.

The CFQ was developed to assess cognitive function using daily life activities and does not have a cutoff for normal function. It is recommended to perform the CFQ in generally comparable groups and to compare scores on a group level. The CFQ is a retrospective instrument subject to the limitations of human memory. It has been reported to change after severe physical stress or trauma such as a brain injury and might be affected by a severe disease such as preeclampsia. However, since there was no difference between groups, this does not seem to be apparent before onset of disease in this population. The CFQ has been designed to be used in a high-income setting.[18] Yet, the CFQ is the most commonly used assessment for

TABLE 1 Maternal characteristics and pregnancy outcomes of the study population

	Eclampsia	Pulmonary edema	Preeclampsia without severe features	Normotensive pregnancy
n	61	28	38	26
Maternal age, years (SD)	22.5 (6)	27.6 (7)	25.7 (6)	28.9 (6)
Race, n (%)				
Black	40 (66)	21 (75)	26 (62)	13 (50)
Colored	21 (34)	7 (25)	12 (38)	12 (46)
White	0 (0)	0 (0)	0 (0)	1 (4)
Marital status, n (%)				
Cohabitating	31 (51)	20 (71)	19 (50)	15 (58)
Single	30 (49)	8 (29)	19 (50)	11 (42)
Education				
Years (SD)	10.6 (2)	10.8 (2)	11.1 (2)	10.7 (2)
>10 years of education, n (%)	36 (59)	17 (61)	29 (76)	18 (69)
>16 years of education,[a] years (SD)	10.9 (1)	10.9 (2)	11.1 (2)	10.7 (2)
Job situation, n (%)				
Working	16 (26)	12 (43)	14 (37)	8 (31)
Student	18 (30)	2 (7)	8 (21)	2 (8)
Unemployed	27 (44)	14 (50)	16 (42)	16 (61)
Living conditions, n (%)				
House or apartment	34 (56)	14 (50)	23 (61)	17 (65)
Informal settlement	27 (44)	14 (50)	15 (39)	9 (35)
Nulliparous, n (%)	43 (71)	10 (36)	20 (53)	5 (19)
HIV positive, n (%)	7 (12)	6 (21)	6 (16)	5 (19)
Smoker, n (%)	11 (18)	2 (7)	1 (3)	2 (8)
Alcohol use, n (%)	7 (12)	0 (0)	1 (3)	0 (0)
Metamphetamine use, n (%)	3 (6)	1 (5)	0 (0)	0 (0)
Diabetes, n (%)	0 (0)	0 (0)	1 (2.7)	0 (0)
Chronic hypertension, n (%)	4 (7)	2 (7)	6 (16)	0 (0)
Anemia, n (%)	0 (0)	1 (5)	3 (7.9)	4 (15)
Depression, n (%)	2 (4)	0 (0)	2 (5.3)	1 (4)
GA at delivery, weeks (SD)	33.1 (5)	31.6 (5)	34.0 (4)	36.7 (4)
Mode of delivery, n (%)				
Vaginal delivery	23 (38)	7 (25)	13 (34)	4 (16)
Planned cesarean section	0 (0)	2 (7)	2 (5)	18 (69)
Emergency cesarean section	38 (62)	19 (68)	23 (61)	4 (16)
Postpartum hemorrhage, n (%)	9 (15)	2 (7)	3 (8)	1 (4)
Coagulation disorder (%)	8 (13)	2 (7)	1 (3)	1 (4)
Delivery–discharge, days (SD)	8.0 (5)	9.0 (5)	4.2 (3)	3.7 (5)
Other organ impairment, n (%)				
HELLP	16 (26)	5 (18)	0 (0)	0 (0)
Renal impairment	11 (18)	4 (14)	0 (0)	0 (0)
Dialysis	1 (2)	1 (4)	0 (0)	0 (0)
Neonatal outcome (%)				
Discharged home	20 (33)	8 (29)	17 (45)	22 (85)

(Continues)

TABLE 1 (Continued)

	Eclampsia	Pulmonary edema	Preeclampsia without severe features	Normotensive pregnancy
Transferred to neonatal unit	28 (46)	13 (46)	17 (45)	4 (15)
Termination of pregnancy	5 (8)	5 (18)	3 (8)	0 (0)
Stillborn	8 (13)	2 (7)	1 (3)	0 n

Values are presented as means (standard deviation) and numbers (percentage).

GA, gestational age; HELLP, hemolysis, elevated liver enzymes, and a low platelet count syndrome; HIV, human immunodeficiency virus, SD; standard deviation.

[a]Restricted population to women above 16 years of age.

TABLE 2 Results of cognitive assessments (Cognitive Failure Questionnaire and Montreal Cognitive Assessment) of women with eclampsia, pulmonary edema and preeclampsia without severe features compared with women with normotensive pregnancies

		CFQ (95% CI)	*P* value	CFQ (95% CI)	*P* value		MoCA (95% CI)	*P* value	MoCA (95% CI)	*P* value
		Mean score		EMM		n	Mean score		EMM	
			.45		.54			<.001		<.001
Eclampsia	56	33.7 (29.9-37.5)	>.99[a]	32.3 (28.1-36.5)	>.99[a]	53	21.6 (20.4-22.7)	<.001[a]	21.7 (20.5-22.9)	<.05[a]
Pulmonary edema	25	28.5 (22.8-34.2)	>.99[a]	27.3 (21.2-33.4)	>.99[a]	26	21.3 (19.7-23.0)	<.01[a]	21.8 (20.0-23.5)	.09[a]
Preeclampsia[b]	34	31.5 (26.6-36.4)	>.99[a]	32.7 (28.1-37.8)	>.99[a]	35	26.4 (25.0-27.8)	>.99[a]	26.1 (24.7-27.6)	>.99[a]
Normotensive	25	30.1 (24.4-35.8)	—	31.5 (24.6-38.4)	—	25	25.8 (24.1-27.4)	—	25.2 (23.2-27.1)	—

Values are presented as means and estimated marginal means with 95% confidence intervals (CI). Results retrieved from robust one-way ANOVA and robust multi-way ANOVA with maternal age, gestational age at delivery, days from delivery to discharge, and parity as continuous covariates and living condition as fixed effect for EMM.

CFQ, Cognitive Failure Questionnaire; EMM, estimated marginal means; MoCA, Montreal Cognitive Assessment.

[a]Pairwise comparisons vs normotensive with Bonferroni correction.

[b]Preeclampsia without severe features.

TABLE 3 Results of subdomains of the Cognitive Failure Questionnaire (CFQ) in women with eclampsia, pulmonary edema, and preeclampsia without severe features compared with women with normotensive pregnancies

	n	Memory	Distractibility	Blunders	Names
P value		.366	.303	.764	.818
Eclampsia	56	9.2 (7.7-10.7)	13.5 (12.0-15.1)	9.4 (8.2-10.7)	2.5 (2.0-3.1)
Pulmonary edema	25	7.2 (5.3-9.1)	11.1 (10.9-14.8)	8.3 (6.5-10.1)	2.6 (1.8-3.7)
Preeclampsia[a]	34	8.4 (7.0-9.8)	12.9 (8.0-17.0)	9.4 (7.8-10.9)	2.2 (1.5-2.9)
Normotensive	25	7.9 (5.7-10.1)	11.8 (9.5-14.1)	9.0 (7.2-10.8)	2.2 (1.4-3.0)

Values are presented as means with 95% confidence intervals. Results retrieved from robust ANOVA.

[a]Preeclampsia without severe features.

cognitive function after preeclampsia.[17,19,20] In our study, many of the participants live in poverty and some of the items on the CFQ were not applicable. Examples include questions such as "Do you find yourself forgetting why you went from one part of/room in the house to the other?" Many of the women in our study live in a single room where they sleep and eat. "Do you find yourself forgetting what you came to the shop to buy?" was also problematic as many answered that they always only buy white bread. Although this may have influenced the outcomes, the groups were comparable.

The MoCA test was also developed in a high-income setting and a score of 26 points is the cutoff for normal cognitive function.[14] In our population, even though women with normotensive pregnancies and preeclampsia without severe features scored higher, the mean scores in these groups were 25.8 and 26.1 points, respectively, which correlates with borderline normal cognitive function. In a cross-sectional study examining 370 healthy 18-year-old South African males and females, the optimal cutoff for sensitivity and specificity to detect cognitive impairment through the MoCA test was 24 points.[21] Thus, women with normotensive pregnancies and noncomplicated preeclampsia in our study scored above the suggested cutoff for cognitive impairment, whereas women with severe preeclampsia, and in particular eclampsia, scored below the limit

TABLE 4 Results of subdomains of Montreal Cognitive Assessment (MoCA) in women with eclampsia, pulmonary edema and preeclampsia without severe features compared with women with normotensive pregnancies

	n	Visuospatial	Naming	Attention	Language	Abstraction	Delayed recall	Orientation
P value		.059	.151	<.001	<.001	<.01	<.001	<.01
Eclampsia	53	3.3 (3.0-3.6)	2.4 (2.2-2.6)	4.1 (3.8-4.5)	1.4 (1.1-1.6)	1.1 (0.9-1.3)	3.0 (2.6-3.5)	5.4 (5.2-5.6)
Pulmonary edema	26	3.5 (3.1-4.0)	2.2 (1.9-2.5)	3.9 (3.4-4.3)	1.5 (1.2-1.9)	1.2 (0.9-1.5)	2.7 (2.0-3.3)	5.8 (5.5-6.1)
Preeclampsia[a]	35	4.0 (3.6-4.3)	2.7 (2.4-2.9)	5.2 (4.8-5.7)	2.3 (2.0-2.7)	1.6 (1.3-1.9)	4.2 (3.7-4.8)	5.8 (5.6-6.1)
Normotensive	25	3.8 (3.4-4.2)	2.5 (2.2-2.8)	5.1 (4.6-5.6)	2.4 (2.1-2.8)	1.5 (1.2-1.8)	3.8 (3.1-4.4)	5.9 (5.6-6.2)

Values are presented as means with 95% confidence intervals. Results retrieved from robust ANOVA.

[a]Preeclampsia without severe features.

of normal cognitive function. Many of the women with preeclampsia with severe features, including all those with eclampsia, were treated with magnesium sulfate for neuroprotection during their hospital stay. Magnesium sulfate has been shown to improve cognitive function in pregnant women.[22] However, magnesium sulfate was not administered at the time of testing and scores were generally lower in women who had undergone treatment with magnesium sulfate (predominately women with eclampsia).

Even though the total sample size is in accordance with previous similar studies of cognition after preeclampsia, this study included a considerable number of women with severe disease, which enabled us to assess different phenotypes of preeclampsia. It is difficult in high-income countries to perform assessments in women with severe disease such as eclampsia, as the incidence is low, around 5/10 000.[23] Performing this study in our setting, where eclampsia is more prevalent, enabled us to recruit this cohort in a short period. Validated tests which included both subjective and objective cognitive function assessments were used. We also assessed cognition before and after delivery using different methods. To our knowledge, this study is the first to examine cognitive function in close proximity to onset of preeclampsia.

Our study does have limitations. Women with preeclampsia with severe features may have been more tired at the time of cognitive function testing. We tried to correct for this by adjusting for "time from delivery to discharge" in the analyses. In addition, no testing for anxiety or depression was performed. However, very few women reported symptoms suggestive of depression during pregnancy. In addition, we adjusted for gestational age as a proxy for maternal and neonatal complications that could be related to anxiety and depression postpartum. The group of women with pulmonary edema was small, introducing the risk of a type 2 error in the analyses where the differences in MoCA test were attenuated after adjustment for confounders. There was no follow up after discharge. Women who deliver at Tygerberg Hospital often live in informal settlements and it is challenging for them to return for follow-up visits due to social circumstances. Finally, women rated their cognitive function prior to diagnosis or delivery retrospectively when doing the CFQ assessment, which could introduce bias. However, the CFQ is the most common test used in the field and our results are comparable to previously published studies.

5 | CONCLUSION

Preeclampsia with severe features such as eclampsia and pulmonary edema may inflict an insult on the brain resulting in poorer cognitive performance close in time to the onset of disease. These findings need be confirmed in other populations and in greater detail. Further research is also needed to assess whether these findings are reversible or if they persist and worsen. The cognitive impairment now found at the time of a severe hypertensive disorder in pregnancy might play a role in the pathway toward the development of cerebrovascular diseases such as stroke and vascular dementia in these women.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet*. 2016;387:999-1011.
2. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170:1-7.
3. Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. *BMJ*. 2018;363:k4109.
4. Nerenberg KA, Park AL, Vigod SN, et al. Long-term risk of a seizure disorder after eclampsia. *Obstet Gynecol*. 2017;130:1327-1333.
5. 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;156:918-930.
6. Postma IR, Slager S, Kremer HP, de Groot JC, Zeeman GG. Long-term consequences of the posterior reversible encephalopathy syndrome in eclampsia and preeclampsia: a review of the obstetric and nonobstetric literature. *Obstet Gynecol Surv*. 2014;69:287-300.

7. Porcel J, Feigal C, Poye L, et al. Hypertensive disorders of pregnancy and risk of screening positive for posttraumatic stress disorder: a cross-sectional study. *Pregnancy Hypertens*. 2013;3:254-260.
8. Elharram M, Dayan N, Kaur A, Landry T, Pilote L. Long-term cognitive impairment after preeclampsia: a systematic review and meta-analysis. *Obstet Gynecol*. 2018;132:355-364.
9. Dayan N, Kaur A, Elharram M, Rossi AM, Pilote L. Impact of preeclampsia on long-term cognitive function. *Hypertension*. 2018;72:1374-1380.
10. Myatt L, Redman CW, Staff AC, et al. Strategy for standardization of preeclampsia research study design. *Hypertension*. 2014;63:1293-1301.
11. NICE. Hypertension in pregnancy: diagnosis and management nice.org.uk2019. www.nice.org.uk/guidance/ng133
12. 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.
13. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol*. 1982;21:1-16.
14. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695-699.
15. Aukes AM, Wessel I, Dubois AM, Aarnoudse JG, Zeeman GG. Self-reported cognitive functioning in formerly eclamptic women. *Am J Obstet Gynecol*. 2007;197(4):365.e1-365.e6.
16. Postma IR, Bouma A, de Groot JC, Aukes AM, Aarnoudse JG, Zeeman GG. Cerebral white matter lesions, subjective cognitive failures, and objective neurocognitive functioning: a follow-up study in women after hypertensive disorders of pregnancy. *J Clin Exp Neuropsychol*. 2016;38:585-598.
17. Baecke M, Spaanderman ME, van der Werf SP. Cognitive function after pre-eclampsia: an explorative study. *J Psychosom Obstet Gynaecol*. 2009;30:58-64.
18. Dockree PM, O'Keeffe FM, Moloney P, et al. Capture by misleading information and its false acceptance in patients with traumatic brain injury. *Brain*. 2006;129:128-140.
19. Aukes AM, Vitullo L, Zeeman GG, Cipolla MJ. Pregnancy prevents hypertensive remodeling and decreases myogenic reactivity in posterior cerebral arteries from Dahl salt-sensitive rats: a role in eclampsia? *Am J Physiol Heart Circ Physiol*. 2007;292:H1071-H1076.
20. Postma IR, Groen H, Easterling TR, et al. The brain study: cognition, quality of life and social functioning following preeclampsia. An observational study. *Pregnancy Hypertens*. 2013;3:227-234.
21. Beath N, Asmal L, van den Heuvel L, Seedat S. Validation of the Montreal cognitive assessment against the RBANS in a healthy South African cohort. *S Afr J Psychiatr*. 2018;24:1304.
22. Rana S, Lindheimer M, Hibbard J, Pliskin N. Neuropsychological performance in normal pregnancy and preeclampsia. *Am J Obstet Gynecol*. 2006;195:186-191.
23. Andersgaard AB, Herbst A, Johansen M, et al. Eclampsia in Scandinavia: incidence, substandard care, and potentially preventable cases. *Acta Obstet Gynecol Scand*. 2006;85:929-936.

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