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Postma, Ineke Rixt; Bouma, Anke; Ankersmit, Iefke Froukje; Zeeman, Gerda Geertruida

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OBSTETRICS

Neurocognitive functioning following preeclampsia and eclampsia: a long-term follow-up study

Ineke Rixt Postma, BSc; Anke Bouma, PhD; Iefke Froukje Ankersmit, MSc; Gerda Geertruida Zeeman, MD, PhD

OBJECTIVE: Women who suffered preeclampsia and eclampsia may report subjective cognitive difficulties in daily life, the interpretation of which is cumbersome, because these are affected by emotional factors. Previous studies only included preeclamptic women investigated shortly after pregnancy. We aimed to determine whether these subjective reports of cognitive difficulty could be interpreted as reflecting objective cognitive dysfunction. Therefore, cognitive functioning was assessed using standardized neurocognitive tests in both preeclamptic and eclamptic women several years following the index pregnancy.

STUDY DESIGN: Forty-six formerly eclamptic, 51 formerly preeclamptic, and 48 control women who had normotensive pregnancies, age-matched, participated in this study. Average elapsed time since index pregnancy was 7 years. Neurocognitive tests were divided into 6 domains; visual perception, motor functions, working memory, long-term memory, attention, and executive functioning. Subjective cognitive functioning was measured by the Cognitive Failures Questionnaire and anxiety/depression by the Hospital Anxiety and Depression Scale.

RESULTS: Both preeclamptic and eclamptic women performed worse on the motor functions domain ($P < .05$), without differences on the other domains. They scored worse on the Cognitive Failures Questionnaire ($P < .01$), the Hospital Anxiety and Depression Scale anxiety ($P < .01$), and depression ($P < .05$) subscales.

CONCLUSION: Women who suffered eclampsia and/or preeclampsia demonstrate no objective cognitive impairment as compared with controls. Contrary to the well-structured test setting, both groups do report more cognitive failures, which are thought to reflect neurocognitive dysfunction in complex, stressful daily-life situations. Such report of cognitive failures may be compounded by anxiety and depression. Future studies should focus on the relationship of neurocognitive functioning with structural cerebral abnormalities.

Key words: anxiety and depression, cognitive complaints, eclampsia, neurocognitive functioning, preeclampsia

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Women who suffered preeclampsia and/or eclampsia report cognitive problems years after the index pregnancy.[1,2] Although the actual prevalence of subjective cognitive difficulties is unknown, they appear to be related to memory, concentration, and vision-related tasks of everyday life.[1-4]

In general, the validity of such subjective reports of cognitive functioning remains controversial, because they are also strongly influenced by noncognitive factors such as symptoms of anxiety and depression.[5,6] Preeclamptic women may exhibit such psychopathology after the experience of a complicated pregnancy.[7-9] Alternatively, women who suffered (pre) eclampsia may have structural brain abnormalities, such as white matter lesions, potentially causing neurocognitive dysfunction.[10-14]

Two small studies evaluated neurocognitive test performance in preeclamptic (but not eclamptic) women within 1.5 years after the index pregnancy and found impairment on some, but not on all cognitive tests.[8,15] Another small study found no evidence for impaired executive functioning and sustained attention.[16]

From the Department of Obstetrics and Gynecology, University Medical Center Groningen (Ms Postma and Dr Zeeman), and Department of Clinical and Developmental Neuropsychology (Dr Bouma and Ms Ankersmit), University of Groningen, Groningen, The Netherlands.

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Because longer follow-up of neurocognitive performance is lacking, we aimed to study cognitive functioning in a relatively large group of women who had preeclampsia and eclampsia using standardized neurocognitive tests and relate this to self-reported cognitive dysfunction and measures of anxiety and depression. We hypothesized that eclamptic women will demonstrate worse performance compared with preeclamptic women, and that both groups would perform worse than controls. Because other studies focused on more limited subdomains of cognitive functioning, we chose to cover a broader range of neurocognitive functions including tasks associated with the posterior brain areas (eg, visual functioning tasks) as well as the frontal brain areas (eg, attention and executive functioning).

Materials and Methods

Participants

All eclamptic, preeclamptic, and control women with normotensive pregnancies, who were enrolled in a previous follow-

up study, received a new invitation.[10,11] Recruitment and selection criteria have been published previously.[10,11,14] Eclampsia and preeclampsia were defined according to international criteria.[17] Preeclampsia was defined as de novo hypertension after 20 weeks' gestation and properly documented proteinuria. Eclampsia was defined as new onset of seizures in women with preeclampsia. Early-onset (pre)eclampsia was defined as indicated delivery <34 weeks' gestational age. Medical records were reviewed for accurateness of diagnosis and to extract clinical and demographic characteristics. This project was approved by the University Medical Center Groningen Institutional Review Board and all women signed informed consent. Measurements were performed between November 2008 and January 2012.

Exclusion criteria were epilepsy, a known cerebrovascular accident, demyelinating disorders, intracranial infections, a history of any cranial neurosurgic procedure, the inability to understand Dutch, or pregnancy at the moment of testing. Women who indicated the presence of a mood disorder were not excluded. For all women, elapsed time since the index pregnancy had to be at least 12 months. Of the 63 eclamptic women who participated in the previous studies,[10,11,14] 48 (76%) could be contacted again and were willing to participate in the present study. Of the 74 preeclamptic and 75 parous control participants participating in previous studies,[10,11,14] respectively, 47 (64%) and 43 (57%) could be contacted again and were willing to participate. Four preeclamptic women who delivered in other hospitals and who had heard about the study requested to participate in the current study, which was allowed. Six additional control participants were included. During the study, 2 eclamptic women were excluded as they showed signs of malingering or underachievement. This was evaluated by the Amsterdam Short-Term Memory (ASTM) test, a symptom validation test presented as a short-term memory task.[18,19] The ASTM test is a valid, standardized, and widely used test to indicate malingering. Excluding these women did not significantly alter the results. One control was excluded because she had professional knowledge of the neurocognitive tasks. Forty-six eclamptic women, 51 preeclamptic women, and 48 controls remained available for analysis.

Age and level of education were similar in the 3 groups (Table 1). Education level was categorized according to the system of Verhage as described by Bouma[19] (1 being the lowest [less than primary school], and 7 the highest [academic degree, such as bachelor/master]). None of the women were in the low education group (category 1 or 2). Average was defined as category 3-5 and as high as category 6-7. The Dutch Adult Reading Test (DART; Dutch version of the National Adult Reading Test) was used to determine premorbid intelligence.[19,20] The DART is a valid, standardized test based on the assumptions that reading ability (of irregular words) is relatively independent of brain disorders, and that it is a strong predictor of intelligence in the normal population.[19,20] No significant difference was found between the groups. One participant had sufficient knowledge of the Dutch language to fulfil the tasks, but the

TABLE 1
Overview of participant characteristics

Characteristic	Eclampsia (n = 46)	Preeclampsia (n = 51)	Controls (n = 48)	*P* value
Age, y	39 (6.5)	39 (6.7)	40 (7.3)	.56
White, n (%)	44 (96)	51 (100)	46 (96)	.40
Elapsed time since index pregnancy, y	8 (2-20)	6 (1-18)	6 (1-27)	.02
Birthweight, g	1310 (300-4440)	1960 (310-4470)	3600 (2210-4620)	< .01
EGA at delivery, wk	32 (22-42^{+1})	34^{+4} (26^{+2}-41)	40 (36^{+2}-40^{+2})	< .01
SGA <10th percentile, n (%)	14 (30)	20 (39)	4 (8)	< .01
Early-onset (pre)eclampsia <34 wk, n (%)	28 (61)	24 (47)		
Nulliparous at index pregnancy, n (%)	40 (87)	34 (67)	21 (44)	< .01
Level of education, n (%)				
Average	18 (39)	24 (47)	18 (38)	.59
High	28 (61)	27 (54)	30 (63)	
DART IQ	99 (11.1)	98 (10.7)	99 (10.5)	.87
Antidepressants, n (%)	0 (0)	6 (12)	2 (4)	.99

Results are expressed as mean (SD), median (min-max), or number (percentage).

DART, Dutch Adult Reading Test; *EGA*, estimated gestational age; *SGA*, small for gestational age.

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DART could not be administered. Another participant was unable to complete the DART because of dyslexia. The population in the northern part of the Netherlands is predominantly white, as was our study population.

Cognitive Failures Questionnaire (subjective cognitive functioning)

The Cognitive Failures Questionnaire (CFQ) evaluates the number of errors committed in the completion of daily tasks.[21] Subjects were asked to complete the questionnaire based on their experiences in the past 6 months. The CFQ consists of 25 items, each scored on a 5-point scale (0-4). The total scale ranges from 0−100, with higher scores indicating more cognitive failures. A cutoff point for the CFQ total score based on the Dutch population was set at ≥44.[22] Three subscales, forgetfulness (8 items), distractibility (8 items), and false triggering (8 items) were derived.[23] Forgetfulness is defined as a tendency to let go from one's mind something known or planned. It includes questions like "Do you read something and find you haven't been thinking about it and must read it again?" Distractibility pertains to social situations or interactions with other people such as being absentminded or easily disturbed and contains questions like "Do you fail to hear people speaking to you when you are doing something else?" False triggering pertains to interrupted processing of sequences of cognitive and motor actions and contains questions like "Do you fail to notice signposts on the road?"

Neuropsychologic tests (objective measures of cognitive functioning)

Participants completed a battery of 16 standardized, reliable, and valid neuropsychologic tests divided into 6 cognitive domains.[19,24] These tests are sensitive to cognitive impairment and have been validated in different populations (normal subjects, neurologic, and psychiatric patients) using different methods (eg, correlational and factor-analytic studies as well as neuroimaging studies). Each cognitive domain consisted of verbal and nonverbal tasks. Tests were administered in a fixed sequence according to standardized instructions for each measure by 2 advanced doctoral students who were well-trained by a neuropsychologist. The battery took approximately 150 minutes to complete (with a 10-minute break halfway). Measures were scored in a standardized fashion outlined in the administration manual of each test.

Visual perception

Visual perception was measured using a Dutch Incomplete Figures Test (GIT-2).[25] Visual processing speed was measured using the Digit Symbol Coding (WAIS-III-NL) test, Symbol Search (WAIS-III-NL)[26] test and the Dutch Stroop Color-Word Test part 1 (word reading) and part 2 (color naming).[27]

Motor functions

Visuomotor speed was measured using the Grooved Pegboard Test[28] for both the dominant and nondominant hand and the Trail Making Test part 5 (Motor Speed; Delis-Kaplan Executive Function System [D-KEFS]).[29]

Working memory

Visuospatial working memory (WM) was assessed using the Corsi Block-Tapping Test (backward and forward version), a total product score was derived from the number of correct sequences and the block span.[30] The task is considered a nonverbal analog to Digit Span (WAIS-III-NL), which was used to measure verbal WM together with the Letter-Number Sequencing Test (WAIS-III-NL).[26]

Long-term memory

Visuospatial long-term memory (LTM) was assessed by the Dutch version of the Location Learning Test (administration procedure II).[31] A total score was derived. Verbal LTM was measured by the Dutch version of the Rey Auditory Verbal Learning Test[32] in which subjects had to learn 15 words in 5 successive trials. A total score was derived.

Attention

Part 1 (visual scanning), part 2 (number sequencing), and part 3 (letter sequencing) of the Trail Making Test (D-KEFS) were used to measure attention.[29] These conditions were designed to quantify key component skills that are required for performing the Number-Letter Switching condition described below.

Executive functioning

Inhibitory control was assessed by part 3 (inhibitory control) of the Dutch Stroop Color-Word Test.[27] Part 4 of the Trail Making Test (Number-letter switching) is similar to 'Part B' of the original Trail Making Test.[29,33] It measures divided attention and cognitive flexibility. Fluency tasks consisted of the Verbal Fluency Test (animals and professions) and the Figure Fluency Test (Dutch version of the Ruff Figure Fluency Test) for visuospatial fluency.[34,35] Planning was measured by the Tower Test (D-KEFS).[29]

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a self-report screening scale that entails 14 items scored on a 4-point scale (0-3).[36] Items were divided into 2 subscales: anxiety and depression, each with a maximum score of 21, with higher scores indicating more symptoms.

Statistical analyses

Statistical analysis was performed using IBM Statistical Package for the Social Sciences version 20 for Windows (IBM Inc, Chicago, IL). Raw test scores were used. Data were checked for normalcy of distribution using distribution curves, Shapiro-Wilk test and Levene's test for homogeneity of variance. Small deviations from a normal distribution because of an outlier were accepted. For measures (Trail Making Test) that were non-normally distributed, logarithmic transformation was used. There were no differences in outcomes between these transformations and nonparametric tests. Patient characteristics were analyzed using Kruskall-Wallis test for nonnormally distributed data and χ^2 test for categoric data. Antidepressant use was analyzed using Fisher's exact test comparing both patient groups with controls. Single imputation was used to

replace 2 missing values in the questionnaire (because of a missed question) and 2 missing values (because of missing test forms) in the tests using estimated means for the whole group. Mean and median values were calculated before and after imputation to ensure the absence of differences. CFQ and HADS outcomes were analyzed using 1-way ANOVA, corrected for elapsed time since index pregnancy, and χ^2 test for cut-off scores. Significant outcomes were further analyzed using a Helmert's contrast (which compares a level with the mean of subsequent levels, ie, controls vs preeclampsia/eclampsia and preeclampsia vs eclampsia), because we hypothesized that both the preeclamptic and the eclamptic group would score worse than controls, and the eclamptic group was expected to score worse compared with the preeclamptic group. Pearson's correlation coefficient was used to describe the relationship between the CFQ and the HADS scores. Multivariate analysis using MANOVA was performed on the different neurocognitive test domains, corrected for elapsed time since index pregnancy. Significant MANOVA results were subsequently tested using univariate analysis (ANOVA). Effect sizes (partial η^2) were calculated to estimate the strength of significant effects between groups.[37] An effect size of partial $\eta^2 = .01$ was defined as small, $\eta^2 = .06$ as medium and $\eta^2 = .14$ as large.[37] To detect a medium effect size of $\eta^2 = .06$ on the multivariate analysis of the test domains for 3 groups, with a power of .80 and alpha of .05, inclusion of 33 (2 test measures) to 45 women (5 test measures) in each group was needed.[38] Multivariable linear regression analyses with backward stepwise inclusion with test outcomes as the dependent variables were performed with group (controls vs preeclampsia and eclampsia), subjective cognitive failures (CFQ) and anxiety/depression (HADS) total score as predictors. We checked for the effect of elapsed time by adding this factor as predictor; however, elapsed time did not significantly change the outcomes of the other predictors. Differences were considered statistically significant at $P < .05$.

RESULTS

Participants

In total, 46 eclamptic women, 51 preeclamptic women, and 48 controls were available for analysis. As shown in Table 1 and as expected, there was a significant difference in gestational age at delivery, birthweight, and the number of small for gestational age children between the groups. Elapsed time since index pregnancy was slightly longer in the eclamptic group compared with the preeclamptic group and controls. Because women with early-onset (pre) eclampsia did not show different results compared with women with late-onset (pre)eclampsia, results for this subgroup are not separately discussed.

Cognitive Failures Questionnaire (subjective cognitive functioning)

When comparing the 3 groups, significant differences were found for the CFQ total score and the subscales forgetfulness, distractibility, and false triggering (Table 2). Using Helmert contrast, scores were significantly worse for preeclamptic and eclamptic women vs controls ($P < .01$), but not between preeclamptic and eclamptic women. The effect size statistics indicate moderate effects. As shown in the Figure, significantly more preeclamptic and eclamptic women compared with controls scored a considerable number of cognitive failures; 24 (52%), 35 (69%), and 8 (17%), respectively ($P < .001$). Cronbach's alpha for the CFQ total score was 0.93, 0.86 for the subscale forgetfulness, 0.84 for distractibility, and 0.83 for false triggering, indicating good reliability.

Anxiety and depression

Significant differences were found for the HADS total score, anxiety, and depression subscales, as shown in Table 2. Using Helmert contrast, eclamptic and preeclamptic women had similar scores, but significantly worse compared with controls ($P < .01$). The effect size statistics indicate moderate effects. Cronbach's alpha was .81 for the HADS anxiety subscale and .80 for the depression subscale. Anxiety and depression subscales were strongly correlated (.62).

TABLE 2
Questionnaires

Questionnaire	Measure	Eclampsia (n = 46)	Preeclampsia (n = 51)	Controls (n = 48)	F (2,142)	Effect size (partial η^2)	*P* value
Cognitive Failures Questionnaire (CFQ)	Total score	43 (16.4)	47 (15.8)	36 (11.0)	6.91	0.089	< .001
	Forgetfulness	16 (5.8)	18 (6.1)	13 (4.1)	8.37	0.104	< .001
	Distractibility	14 (5.8)	15 (5.8)	12 (3.6)	4.34	0.059	.01
	False triggering	12 (5.2)	13 (5.0)	9 (3.9)	7.40	0.095	< .001
Hospital Anxiety and Depression Scale (HADS)	Total score	12 (6.6)	11 (5.8)	8 (5.5)	6.20	0.081	< .005
	Anxiety	7 (3.8)	6 (3.4)	5 (3.1)	6.08	0.077	< .005
	Depression	5 (3.5)	4 (3.4)	3 (2.9)	3.87	0.054	.02

Results are expressed as mean (SD), F:1-way analysis of variance test statistics of between-group effect.

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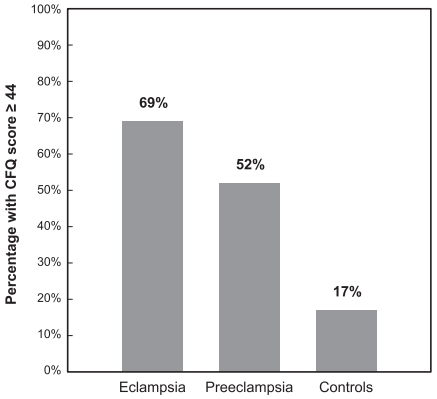
FIGURE
Percentage of participants with cognitive failures



Percentage of formerly preeclamptic and eclamptic women and controls with high cognitive failures questionnaire (CFQ) score (cutoff value of 44). χ^2 (2, n = 145) = 27.8, $P \leq .001$.

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Neuropsychologic tests

Multivariate analysis of neuropsychologic test domains only revealed a significant result for motor functions ($P < .05$) (Table 3) because of a significant difference in visuomotor speed measured by the Trail Making Test part 5 (D-KEFS) ($P < .001$). The effect size statistics indicate small effects except for a medium effect in visuomotor speed. Further analysis of visuomotor speed using Helmert contrast showed that eclamptic women scored worse than preeclamptic women ($P < .05$) and that both patient groups scored worse compared with controls ($P < .01$).

Relationship between CFQ and HADS

Significant correlations between the CFQ total score and the HADS anxiety (0.37) and depression (0.54) scores were found in the total group of participants ($P < .05$ for all coefficients).

Multivariable regression analysis

Multivariable linear regression analyses with backward stepwise inclusion with test outcomes as the dependent variables were performed with group (controls vs preeclampsia and eclampsia), subjective cognitive failures (CFQ), and anxiety/depression (HADS) total score as predictors. Elapsed time since index pregnancy did not significantly change the outcomes of the other predictors. We found that CFQ score was associated with WAIS-III Symbol Search (β − .22, $P < .01$), Trail Making Test part 1 (β .21, P = .01), Grooved Pegboard score nondominant hand (β .20, P = .02), Dutch Incomplete Figures Test (β .22, P = .02), Stroop Color-Word Test part 2 (β .17, P = .04) and part 3 (β .24, P = .003), and the Tower Test (β .18, P = .06). HADS total score was associated with the Corsi Block-Tapping Test (β − .17, P = .04), Dutch Incomplete Figures Test (β − .29, P = .003), Tower Test (β −.27, P = .004), and the WAIS-III Letter-Number Sequencing Test (β − .23, P = .006). Group (controls vs preeclampsia and eclampsia) was not significantly associated with any of the tests, meaning that women with (pre) eclampsia scored similar to controls, but for the Trail Making Test part 5 (β .26, P = .001), as was shown previously in the multivariate analyses (MANOVA).

Comment

This study aimed to assess cognitive functioning using standardized neurocognitive tests in a relatively large group of both formerly preeclamptic and eclamptic women with an average follow-up of 7 years. Aside from minor slowing in motor speed, no differences were seen in objective measures of visual perception, working memory, long-term memory, attention, and executive functioning as compared with controls. Preeclamptic as well as eclamptic women reported significantly more cognitive failures in daily life and scored significantly higher for anxiety and depression, factors that were associated with some, but not all neurocognitive tests. There was no effect of early-onset (pre) eclampsia.

Objective cognitive functioning was the primary outcome of this study. No objective cognitive impairment besides a slightly slower visuomotor speed was found in (pre)eclamptic women compared with controls. Women with eclampsia did not demonstrate worse performance than preeclamptic women. Our findings are consistent with our previous study assessing executive functioning and sustained attention in formerly (pre)eclamptic women.[16] Small studies, at short-term follow-up (within 1.5 years) and only in preeclamptic women, did not show impaired performance on the majority of neurocognitive tests, except for a significantly lower score on an auditory-verbal memory task,[15] on the Digit Symbol Coding Test (WAIS-III) and the Paced Auditory Serial Addition Test (divided attention), which were explained by a difference in posttraumatic stress symptoms.[8]

The present study found no differences in neurocognitive test results, although there was a difference in CFQ score, a measure of self-reported cognitive failures representing daily life conditions. A possible explanation for this lack of agreement between objective neurocognitive tests and subjective cognitive failures is that subtle cognitive differences between (pre)eclamptic women and controls may not come to surface in a well-structured test setting. Such test setting is usually quiet with few distractions, there are clear time points for task initiation and completion, and the subject is asked to complete one task at a time. This is in contrast with daily-life challenges, which are usually unstructured with numerous distractions, all of which require significant cognitive flexibility as well as cognitive self-evaluation and executive control of behavior.[39-42]

The CFQ was developed as a valid self-report instrument to measure the tendency to make mistakes in everyday life. In this study, the CFQ score did show an association with scores on tests measuring visual perception, visuomotor speed, attention and executive functioning, which suggests that the CFQ is indeed related to objective cognitive functioning. On the other hand, we found that the CFQ strongly relates to anxiety and depression. Anxiety and depression were present to a larger extent in (pre)eclamptic women as compared with controls. In the literature, executive functioning, or the control of complex, goal-directed behavior is the cognitive ability, which is most susceptible to

TABLE 3
Multivariate analysis of cognitive domains of neurocognitive tests

Cognitive domain	Function	Test	Measure	Eclampsia (n = 46)	Preeclampsia (n = 51)	Controls (n = 48)	Effect size (partial η^2)	F (2,14)	*P* value
Visual perception							0.025	0.72[a]	.70
	Perceptual closure	Dutch Incomplete Figures Test (GIT-2)	Total score (accuracy)	13 (3.2)	13 (2.7)	13 (3.0)			
	Visual perceptual speed	Digit Symbol Coding (WAIS-III-NL)	Total score (accuracy)	81 (15.2)	83 (11.5)	81 (13.2)			
		Symbol Search (WAIS-III-NL)	Total score (accuracy)	36 (6.8)	38 (6.4)	38 (7.3)			
		Stroop Color-Word Test	Part 1: word reading (time)	44 (7.9)	45 (8.6)	42 (7.9)			
			Part 2: color naming (time)	55 (9.5)	55 (10.3)	54 (8.3)			
Motor functions							0.051	2.53[a]	.02
	Visuomotor speed	Grooved Pegboard	Score dominant hand (time)	66 (10.1)	66 (9.2)	64 (8.5)		0.45	.64
			Score non-dominant hand (time)	74 (9.8)	73 (12.0)	72 (12.5)		0.11	.89
		Trail Making Test (D-KEFS)	Part 5: motor speed (time)	26 (1.5)	22 (1.3)	20 (1.3)		7.22	< .001
WM							0.015	0.73[a]	.63
	Visuospatial WM	Corsi Block-tapping Test	Total product score (accuracy)	97 (25)	101 (30)	108 (26)			
	Verbal WM	Digit Span (WAIS-III-NL)	Total score (accuracy)	15 (3.0)	15 (3.3)	15 (3.7)			
		Letter-Number Sequencing (WAIS-III-NL)	Total score (accuracy)	10 (1.4)	10 (2.0)	11 (2.2)			
LTM							0.015	1.08[a]	.37
	Visuospatial LTM	Location Learning test	Total score (accuracy)	16 (10.5)	18 (16.3)	15 (12.9)			
	Verbal LTM	15-word Learning test	Total score (accuracy)	48 (7.8)	46 (7.0)	47 (8.4)			
Attention							0.012	0.54[a]	.77
	Visual scanning	Trail Making test (D-KEFS)	Part 1: visual scanning (time)	18 (1.3)	19 (1.2)	19 (1.4)			
	Visual scanning and sequencing	Trail Making test (D-KEFS)	Part 2: number sequencing (time)	28 (1.4)	28 (1.3)	27 (1.4)			
			Part 3: letter sequencing (time)	27 (1.3)	26 (1.2)	25 (1.4)			

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(continued)

TABLE 3
Multivariate analysis of cognitive domains of neurocognitive tests *(continued)*

Cognitive domain	Function	Test	Measure	Eclampsia (n = 46)	Preeclampsia (n = 51)	Controls (n = 48)	Effect size (partial η^2)	F (2,14)	*P* value
Executive functioning							0.024	0.69[a]	.73
	Inhibitory control	Stroop Color-Word Test	Part 3: inhibitory control (time)	82 (14.7)	87 (27.9)	81 (16.6)			
	Divided attention and cognitive flexibility	Trail Making Test (D-KEFS)	Part 4: number-letter switching (time)	65 (1.4)	66 (1.3)	62 (1.4)			
	Verbal fluency	Verbal Fluency Test	Total score (accuracy)	45 (8.9)	44 (9.9)	45 (10.9)			
	Visuospatial fluency	Figure Fluency Test	Total score (accuracy)	96 (22.5)	98 (17.8)	101 (17.4)			
	Planning	Tower Test (D-KEFS)	Total performance score (accuracy)	18 (4.2)	19 (3.4)	19 (3.4)			

Results are expressed as mean (SD). Time is in seconds.

LTM, long-term memory; *WM*, working memory.

[a] Multivariate analysis of variance test statistics of between-group effect.

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stress.[39-42] As a consequence, women with (pre)eclampsia who indicate more anxiety and more depressive symptoms may therefore be more vulnerable for cognitive failures in complex, and perhaps more stressful daily life conditions compared with controls.[43] The prevalence of posttraumatic stress disorder seems to be increased following a preeclamptic pregnancy, even after several years.[44-46] Moreover, anxiety and depression in women who had (pre) eclampsia may be a cause, rather than a consequence of experiencing long-lasting cognitive failures in daily life. It is possible that symptoms of anxiety and depression were already present before the index pregnancy, but these were not specifically asked for when including patients into the study. Both depression and anxiety in early pregnancy seem to be associated with the subsequent development of preeclampsia (odds-ratio of 2.5 and 3.2, respectively).[47] The precise biochemical mechanism behind this course of events remains speculative: distress conditions during pregnancy may directly change the hypothalamic-pituitary axis (HPA) resulting in increased cortisol levels and concomitant changes in cellular immunity, associated with hypertension and endothelial dysfunction.[48]

Alternatively, women who had eclampsia or preeclampsia more often demonstrate cerebral white matter lesions on long-term follow-up MRI compared with parous control women.[10,11] One could expect that the presence of such lesions may influence both subjective and objective cognitive functioning. However, nonobstetric studies reveal that subjective complaints at a relatively young age appear to be related to cerebral structural abnormalities, such as white matter lesions, and cognitive decline in later life.[5,6,49] Therefore, it cannot be excluded that the cognitive complaints found in this study are related to white matter lesions, even in patients who did not show objective cognitive disturbances.

The main strength of this study is that it is, to date, the largest study with well-defined groups of formerly preeclamptic and eclamptic women to report both subjective cognitive functioning and

standard neurocognitive test results in the long-term and relate these to emotional factors such as anxiety and depression. There are several limitations to this study, one of which is the lack of prepregnancy information on neurocognitive functioning. In view of the rare incidence of eclampsia, a prospective study design is not feasible. Second, approximately 70% of the women who participated in the study of Aukes et al[10,11] could be contacted again and were willing to participate in the study now reported that may have given rise to selection bias. However, most nonparticipating women could not be contacted because of change of address and/or phone number. Other nonparticipating women mentioned the time and travel burden as the main reason not to participate, although some declined because of fear of confrontation with the traumatic experience of their complicated pregnancy. Third, the wide range in elapsed time since index pregnancy reflects the rare incidence of eclampsia. Despite careful matching, elapsed time since index pregnancy was slightly longer in eclamptic women, however, controlling for elapsed time did not significantly alter the results. Fourth, the effect of subsequent pregnancies following the index pregnancy can not be excluded. Nine women had preeclampsia during a subsequent pregnancy. Last, it was not possible to reliably recruit more previously eclamptic women into this study. In the context of the rare incidence of eclampsia this represents a sizeable study showing results that are clinically important.

In summary, formerly preeclamptic and eclamptic women do not show clear neurocognitive impairment years after the index pregnancy but for minor slowing in motor speed. They express cognitive failures that are thought to reflect neurocognitive dysfunction in complex, and stressful daily-life situations. Such report of cognitive failures may be compounded by symptoms of anxiety and depression. Indeed, the CFQ may be interpreted as a measure of executive control of behavior, in which people with anxiety and depression experience cognitive failures mainly in complex and stressful daily life events.[40] In this scheme high levels of stress hormones seem detrimental for executive control and make a person susceptible for cognitive failures.[41] Moreover, they might be an indicator for development of cognitive dysfunction at older age. Either way, subjective cognitive difficulties in such a young cohort of women should be taken seriously and these women deserve long-term follow-up.

Future studies should focus on the relationship between subjective and objective neurocognitive functioning, symptoms of anxiety and depression and brain white matter lesions. Follow-up studies (ie, 20-30 years) would provide insight whether there is a relationship between (pre)eclampsia and subjective cognitive difficulties earlier in life and dementia and cerebrovascular disease later in life. ■

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