The maternal brain in (pre)eclampsia

Long-term neurocognitive functioning

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INTRODUCTION

1

Preeclampsia and eclampsia

Preeclampsia is a hypertensive, multisystem disorder of pregnancy, which is a leading cause of maternal and fetal/neonatal morbidity and mortality. It is defined as new-onset hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) combined with proteinuria after the 20th week of pregnancy.[1] Eclampsia is defined as the occurrence of tonic-clonic convulsions in a woman with preeclampsia. The overall worldwide estimates of the incidence of preeclampsia and eclampsia are 4.6% and 1.4% of all deliveries, with an incidence in the Netherlands of 3.3% and 0.1% respectively.[2] In developing countries, incidence is considerably higher, up to 15.6% and 4.0% respectively for preeclampsia and eclampsia.[2] Preeclampsia was the leading cause of maternal mortality in the Netherlands between 1993 and 2005, with a ratio of 3.5 per 100,000 live births (overall maternal mortality 12.1 per 100,000 live births). Eclampsia complicated 44% of these cases, and cerebral haemorrhage (45%) was the leading mode of death.[3]

The central nervous system can be involved during the course of preeclampsia in the form of hyperreflexia, headaches, visual disturbances, mental status changes and eclampsia. The ancient writings of the Egyptians, Chinese and Indians already make mention of eclampsia.[4] The Greek described it as follows: 'In pregnancy, the onset of drowsy headaches with heaviness is bad; such cases are perhaps liable to some sort of fits at the same time.' They named this phenomenon "eclampsia", derived from the Greek word, "eklampsis", which means "shining forth" or "sudden flashing". Until 1739, eclampsia was seen as a form of epilepsia. In the second half of the 18th century, eclampsia was recognized as a separate entity: first, it was thought eclamptic fits could develop due to uraemia, but other substances were also proposed to be the toxic initiator. At that time, the term toxaemia originated and treatment consisted of phlebotomy and purgation. In 1906, treatment with magnesium sulphate was introduced by Horn, which drastically changed the management of (pre)eclampsia.[4-6]

Although the pathophysiology of preeclampsia remains enigmatic, more information has become available throughout the years. Through the examination of placental bed biopsies, Robertson & Brosens et al.[7,8] were the first to pose that preeclampsia is associated with shallow trophoblast invasion and a subsequent reduction in placental perfusion. Roberts et al. in 1989[9] postulated that preeclampsia is an endothelial cell disorder and that the reduction in placental perfusion causes release of damaging factors into the maternal circulation. The currently leading hypothesis is that these factors may lead to a maternal inflammatory response and generalized endothelial dysfunction, which alters the vascular reactivity.[6,10] A two-stage model is proposed; the first stage consisting of poor placentation resulting in release of substances by the placenta which enter the maternal circulation, the second stage consisting of the effect of these substances (combined with constitutional maternal health factors) on the maternal circulation.[11]

Cerebral consequences of (pre)eclampsia

Posterior Reversible Encephalopathy Syndrome

The pathophysiology of eclampsia has not been completely elucidated. Two theories have been proposed for the development of eclamptic seizures: the *underperfusion* versus the *overperfusion* theory. Endothelial dysfunction and failure of autoregulation of cerebral blood flow is thought to play a role in both. Under normal conditions, with intact cerebrovascular autoregulation, an increase in systemic blood pressure leads to higher arteriolar resistance in the brain through adaptation of vessel diameter. This mechanism causes the brain to maintain a relatively constant blood flow during changes in perfusion pressure. In the *underperfusion* theory, "overautoregulation" of the cerebral vasculature in the setting of hypertension is hypothesized, resulting in vasospasm, which subsequently leads to ischaemia, infarction and cytotoxic edema. This theory is based on angiographic narrowing of cerebral blood vessels that have been observed in eclampsia.[12,13] Currently, focus is shifted more towards the *overperfusion* theory. This theory poses that a combination of endothelial dysfunction and an increase in blood pressure results in failure of autoregulation of cerebral blood flow. This may subsequently give rise to both vasoconstriction and forced vasodilatation in different regions of the brain (the so-called 'sausage string phenomenon').[14,15] Hyperperfusion and consequently vasogenic edema develop, with a predilection for the posterior parietal areas of the brain.[16-19] Because normal cerebral autoregulation requires an intact vascular endothelium, breakthrough of the blood brain barrier may also occur in the setting of mild hypertension and endothelial damage.[20,21]

In the scheme of this *overperfusion* theory, an eclamptic seizure and the acute phase following this seizure are considered a form of the Posterior Reversible Encephalopathy Syndrome (PRES); several studies have shown that PRES is seen in nearly all eclamptic patients.[22-24] PRES is considered a reversible neurotoxic and neurometabolic condition characterized by a typical clinico-radiological syndrome, first described by Hinchey et al. in 1996.[25] Computed Tomography (CT) features in PRES include either hypodense areas consistent with edema or no specific abnormalities, and magnetic resonance imaging (MRI) shows a characteristic pattern of hyperintense areas consistent with edema, predominantly in the white and gray matter of parietal and occipital lobes.[26,27] In PRES, cerebral edema is thought to be predominantly vasogenic by nature.[22,23,28] Vasogenic edema occurs when there is breakthrough of the blood brain barrier with allows intravascular proteins and fluid to penetrate into the parenchymal extracellular space. PRES has also been associated with numerous systemic conditions in non-obstetric patients of all age categories, such as systemic lupus erythematosus, acute glomerulonephritis and immunosuppressive therapy.[29-31] The exact mechanism leading to cerebral edema in PRES is not understood, but it is hypothesized that hypertension and endothelial dysfunction play a synergistic role.

The distribution of cerebral edema in PRES may be related to local levels of perfusion in vascular watershed areas or regions with mainly end-arterial vascular supply. In addition, cerebral vessels have an extensive sympathetic neural supply, stimulation of which will increase the upper limit of autoregulation. This sympathetic innervation is less pronounced in the posterior arteries.[26,28]

Both (pre)eclampsia and PRES have long been held to be entirely reversible disorders without any consequences for future health.[25,32] However, this reversibility has recently been questioned for both conditions.[29,33] The cerebral vasogenic edema which can be seen during the acute moment of eclampsia and PRES usually resolves, but in addition, cytotoxic edema can be demonstrated in a considerable number of patients. Cytotoxic edema occurs due to a disruption in cellular metabolism, leading to cellular retention of sodium and water and subsequent swelling of the cells. It has been suggested that vasogenic interstitial edema can progress to the extent that it may cause decreased regional perfusion to ischaemic levels resulting in cytotoxic edema. Imaging abnormalities are described after eclampsia and PRES several weeks after the resolution of clinical symptoms.[23,34] The persistence of such abnormalities and their possible consequences remains to be elucidated. Available studies on long-term consequences of PRES are reviewed in **chapter 2**.

Cerebral white matter lesions

While edema (PRES) is seen in eclampsia in the acute phase, on long-term (several years) follow-up this edema has disappeared. Neuroimaging studies which were carried out several years after (pre)eclampsia revealed cerebral white matter lesions (WML), or hyperintensities. Women who suffered eclampsia (41%) or preterm (< 37 weeks) preeclampsia (47%) demonstrated WML more often and more extensive compared to women with term preeclampsia (14%) and control women who had a normotensive pregnancy (21%).[35,36] These atypical WML are located mostly in the frontal areas of the brain.[37] At first, it was hypothesized that these WML may be a direct consequence of the PRES episode. Vasogenic edema may progress to such an extent that regional cerebral perfusion pressure decreases to ischaemic levels leading to areas of cytotoxic edema in severe cases. This cytotoxic edema may later appear as infarctions or WML on MRI.[35,38] Several findings contradict this hypothesis; 1) WML in formerly eclamptic and preeclamptic women are mainly located in the frontal areas of the brain instead of the occipito-parietal lobes, the most common location for PRES,[37] 2) WML are not only found in eclamptic women, but also in a significant percentage of women who suffered preeclampsia who are generally not thought to have experienced PRES (although some of them may also have experienced PRES without seizures[39]). Therefore, it is not plausible to hold PRES solely responsible for the development of white matter lesions in these women. If and to what degree the presence of PRES in formerly eclamptic women contributed to the development of WML is unknown. Neuroimaging is generally not performed in the acute phase of (pre)eclampsia

and information on possible preexisting presence of WML is lacking.[35,36]

WML are non-specific neuroimaging findings and little is known about their causes, the prevalence and the exact clinical importance in younger individuals of childbearing age. The few available studies have been performed in the elderly population. Postmortem studies in elderly subjects demonstrate that cerebral WML show a hypoxic response, arteriolar sclerosis, amyloid angiopathy and reduced endothelial vascular integrity, suggesting the pathogenesis of such WML to evolve around chronic hypoperfusion.[40,41] In the middle-aged and older population, the presence and development of WML are associated with vascular risk factors and the presence of hypertension.[42,43]

WML are considered part of the continuum of neuroimaging features representing cerebral small vessel disease, together with lacunar infarction and cerebral microbleeds.[44] Cerebral small vessel disease, or cerebral microangiopathy, is a term used for a syndrome of clinical, cognitive and neuroimaging findings which are thought to arise from affected perforating arterioles, capillaries and venules resulting in brain damage.

Prevalence of WML in the elderly (e.g. 70 years or over) is high (up to 99%).[45-48] In younger individuals (< 40 years of age), prevalence has been reported to range from 0.5% to 32%[49-55] and in individuals age 60-70, prevalence rates of 22.7% to 100% have been described.[49,56-58] In the elderly, WML have been associated with cognitive decline, stroke and dementia.[45,59-61]

In **chapter 6 and 7** of this thesis another possible explanation for the presence of WML in formerly (pre)eclamptic women is discussed, which is independent of pregnancy in and of itself. WML may be an early expression of a constitutional susceptibility for cardiovascular and cerebrovascular disease.[36,42,43] Endothelial vascular disorders and hypertension, found to be related to WML in the elderly, are also present in (pre)eclamptic women. Preeclampsia and atherosclerosis are both associated with similar risk factors such as chronic hypertension, obesity, metabolic syndrome and insulin resistance.[62] Microvascular dysfunction may be the predominant mechanism for both cardiovascular disease and preeclampsia as women with preeclampsia have higher risk of cardiovascular events and stroke later in life.[63,64] Preterm preeclampsia seems to be related to an even greater risk for cardiovascular disease in later life.[63] Therefore, pregnancy could be considered an early stress test for the cardiovascular system. Women at risk might not be able to optimally compensate for the vascular challenges associated with pregnancy and subsequently develop preeclampsia.[65] Both WML and preeclampsia may therefore be consequences of a constitutional susceptibility of cardiovascular disease. Consequently, WML may develop independent of, and may have been present prior to pregnancy.

Whether the WML found in formerly preeclamptic and eclamptic women are associated with cognitive impairment is currently unknown and investigated in **chapter 5 and 6**.

Cognitive functioning following (pre)eclampsia

In general, shortly postpartum (up to several months), women frequently report cognitive deficits which are clustered under the terms 'mommy brain' or 'maternal amnesia'. It has been shown that recently postpartum women show a small, but significant, impairment on some measures of cognition that place relatively high demands on executive cognitive control.[66-68] Although not much is known about short-term postpartum cognitive functioning following a pregnancy complicated by (pre)eclampsia, preeclamptic women do not seem to be more cognitively impaired compared with normotensive women.[69] These cognitive deficits described directly postpartum may be viewed from an adaptive perspective; rather than being a negative consequence of pregnancy, these cognitive changes may be seen as cognitive reorganization, in which social cognition which is relevant to maternal or fetal wellbeing is enhanced to the cost of other cognitive tasks.[68]

However, clinical experience learns that formerly preeclamptic women may complain of memory and concentration problems up until years following their pregnancy. Women may seek attention from their general practitioner, obstetrician, a neurologist or psychologist. On short-to-medium term (up to 2 years), self-reported memory complaints in formerly eclamptic women have been described. Using structured telephone interviews in 123 formerly eclamptic women, 18% reported problems with concentrating after 6-24 months.[70] Two pilot studies focused on objective cognitive functioning measured by neurocognitive tests in preeclamptic, but not eclamptic women, on short-to-medium term (within 1.5 years).[71,72] Formerly preeclamptic women scored significantly lower on an auditory-verbal memory task compared to controls[71], which implies impaired word learning capacity. In addition, formerly preeclamptic women seem impaired in visual perception (WAIS III Digit Symbol Coding task) and divided attention (Paced Auditory Serial Addition Test).[72] These studies were performed in small cohorts (n = 10 and n = 29 respectively).

On long-term (several years) follow-up, subjective self-reported cognitive problems are still reported. Women who had preeclampsia reported significantly more loss of memory and/or concentration compared to parous controls 11 months to 9 years later.[73] Aukes et al. evaluated self-reported cognitive functioning in 30 eclamptic, preeclamptic and healthy parous women several years following the index pregnancy. Formerly eclamptic women reported significantly more cognitive failures in life compared to controls, and those who had multiple seizures reported even more.[74] Formerly eclamptic women also scored lower on a vision-related quality of life questionnaire than controls, however none of these women demonstrate visual field loss.[75] Vision-related quality of life impairment in eclamptic women may therefore be related to problems concerning higher-order visual functions. Because cognitive problems in such a young cohort of women, who are in the midst of their lives, are cumbersome and deserve attention, this thesis focusses not only on subjective, but also objective cognitive functioning several years following a (pre)eclamptic pregnancy. Self-reported cognitive problems can be measured

using a questionnaire. In **chapter 3** of this thesis, subjective cognitive functioning following preeclampsia will be studied. Objective cognitive impairment can be measured using neurocognitive tests/tasks. Many standardized test are available for a wide range of cognitive functions.[76,77] In **chapter 4** objective cognitive functioning in the domains of sustained attention and executive functioning is described and in **chapter 5** a broad, standardized cognitive test battery is studied comprising several cognitive domains (visual perception, motor functions, working memory, long-term memory, speed of information processing, attention and executive functioning), measured in both preeclamptic and eclamptic women. Tasks for both the posterior (PRES) and the anterior brain areas are incorporated (WML). Since neuropsychological complaints in daily life and neurocognitive test results may be influenced by emotional aspects such as anxiety and depression[77], this is also studied in **chapter 5**. In **chapter 6** the relationship between subjective and objective cognitive functioning and WML is studied.

Depression and anxiety following preeclampsia

Emotional lability in women during pregnancy and after childbirth is common, since these are major life events requiring many physical but also social adjustments. While most of these complaints are transient and within the normal range of difficulties, the development of mood and anxiety disorders following pregnancy are not uncommon. The overall postpartum rate is approximately 12% for depression disorders and 8% for anxiety disorders.[78]

Psychological aspects following a pregnancy complicated by preeclampsia have been described in the literature: both depression and anxiety disorders have been found, the latter mainly in the form of posttraumatic stress disorder (PTSD).[79] It is known that depression and anxiety often co-occur and are strongly correlated.[80] Most studies have focused on anxiety and depression as a consequence of a preeclamptic pregnancy. Such pregnancies are often associated with interventions and infant hospitalization which might have been experienced as traumatic. Even more so, preeclampsia, and to a larger extent eclampsia, is potentially life threatening for both mother and fetus. Hence, a pregnancy complicated by an eclamptic seizure may be experienced as even more traumatic and may have a larger impact. Only one of the studies performed has focused on this specific group of eclamptic women. Andersgaard et al. found that 14% of these women report depression within 2 years following their pregnancy.[70]

The literature concerning anxiety and depression disorder following preeclampsia is not conclusive; some studies find an increased prevalence while others fail to show this. However, in general the evidence points to positive associations of anxiety and depression with previous preeclampsia, within 1.5 years following pregnancy.[71,72,81-83] Several years following severe early onset preeclampsia with preterm birth, women experience more often posttraumatic stress symptoms compared to women with preterm birth without

preeclampsia.[84]

Whereas the experience of a preeclamptic pregnancy may give rise to depression and anxiety, it is less well known that depression and anxiety itself may also be a risk factor for the development of preeclampsia. Both depression and anxiety in early pregnancy seem associated with the subsequent development of preeclampsia (odds-ratio of 2.5 and 3.2 respectively).[85] The biochemical mechanism behind this course of events has not been revealed so far.

Screening for depressive symptoms and anxiety can be executed using self-report measures. In this thesis, anxiety and depression several years following a (pre)eclamptic pregnancy is studied (**chapter 5**). The relationship of anxiety and depression with subjective cognitive functioning (**chapter 3** and **chapter 5**) and objective cognitive tests (**chapter 5**) is examined as well. The relationship with WML is studied in **chapter 6**.

Aims of this thesis

- To review the literature for long-term consequences of Posterior (Reversible) Encephalopathy Syndrome in eclampsia and preeclampsia and in the non-obstetric population. (**Chapter 2**)

- To assess self-reported cognitive functioning, quality of life and social functioning in a large cohort of formerly preeclamptic women. (**Chapter 3**)

- To evaluate executive functioning and sustained attention in women with a history of eclampsia. (**Chapter 4**)

- To study long-term neurocognitive functioning in a large group of formerly preeclamptic and eclamptic women using objective neurocognitive tests and to determine the relationship with subjective cognitive failures, anxiety and depression. (**Chapter 5**)

- To determine the relationship between neurocognitive functioning and cerebral white matter lesions in formerly preeclamptic and eclamptic women. (**Chapter 6**)

- To assess whether pregnancy in and of itself has a relationship with the presence of WML and subjective cognitive dysfunction. (**Chapter 7**)

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THE BRAIN STUDY: COGNITION, QUALITY OF LIFE AND SOCIAL FUNCTIONING FOLLOWING PREECLAMPSIA; AN OBSERVATIONAL STUDY

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3

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Abstract

Objective: Previously preeclamptic women may express cognitive difficulties, which have largely been unappreciated or attributed to stresses of a complicated pregnancy. This study aimed to explore the scope of perceived neurocognitive and psychosocial problems as well as quality of life following preeclampsia.

Methods: Observational study. Through website promotion and e-mail, registrants of the USA-based Preeclampsia Foundation who experienced preeclampsia in the past 20 years were invited to complete a web-based survey. Participants were requested to ask an acquaintance that had a normotensive pregnancy to also complete the survey (controls). The Cognitive Failures Questionnaire (CFQ), abbreviated WHO Quality Of Life questionnaire (WHOQOL-BREF), Social Functioning Questionnaire (SFQ) and Breslau Short Screening Scale for DSM-IV Posttraumatic Stress Disorder were used in the survey. Analysis was performed using Mann–Whitney U tests and linear regression.

Results: 966 cases and 342 controls completed the survey (median age 34, median time since first pregnancy 4 vs. 5 years). Cases scored significantly worse on CFQ (median 35 vs. 27), WHOQOL-BREF domains physical health (15 vs. 17), psychological (13 vs. 15), social relationships (13 vs. 15) and environment (15 vs. 16), and SFQ (8 vs. 7). All $p < 0.001$. Multivariable analysis showed an independent significant effect of eclampsia on CFQ and of migraine on all questionnaires and the effect of preeclampsia was still present after adjustment for confounders. Posttraumatic stress symptoms accounted for part of the relationships.

Conclusions: Previously preeclamptic women appear to perceive more cognitive and social problems, and report poorer quality of life compared to a group of women with normotensive pregnancies. Research relating to the origin and management of these issues is needed.

Introduction

There is growing recognition that preeclampsia is not a transient event. The syndrome is associated with a greater incidence of hypertension, ischaemic heart disease or stroke later in life.[1] Mechanisms of the increased risk for cardiovascular disease following a pregnancy complicated with preeclampsia remain unknown but risk factors for atherosclerosis such as chronic hypertension, dyslipidemia, obesity and glucose intolerance are likely to play a role. Formerly eclamptic women report cognitive difficulties related to memory and concentration; small studies have not clearly demonstrated these in preeclampsia.[2-7] At long-term follow-up, formerly eclamptic and preeclamptic women may demonstrate cerebral white matter lesions on MRI.[8,9] The presence of both such lesions and chronic hypertension has been associated with cognitive decline in later life.[10-12] Alternatively, a pregnancy complicated by preeclampsia may be experienced as traumatic, resulting in trauma-related psychopathology such as posttraumatic stress syndrome (PTSD) and depressive symptoms, known to influence cognitive functioning[4,13-16] It is therefore possible that both biological constitution as well psychosocial factors are responsible for the neurocognitive difficulties reported by formerly preeclamptic women. We sought to determine the actual scope of cognitive problems and the impact of preeclampsia on quality of life and social functioning. Because few small studies so far have focused on cognitive and social functioning after preeclampsia, we aimed to make an inventory of the nature and extent of these issues in a large cohort of formerly preeclamptic women.

Methods

All registrants of the Preeclampsia Foundation were contacted through the foundation's website (www.preeclampsia.org) and a mass e-mail, explaining the study aims and methodology. The Preeclampsia Foundation is a USA-based non-profit patient advocacy organization established in the year 2000 whose mission is to reduce maternal and infant illness and death due to preeclampsia and other hypertensive disorders of pregnancy, by providing patient support and education, raising public awareness, catalyzing research and improving health care practices. Free registration with the foundation is open to anybody who is interested in preeclampsia, but is mostly sought after by women who experienced the disease. The survey was online between April 29, 2010 and Oct. 4, 2010. At the start of the study, the Preeclampsia Foundation had 8677 registrants. This project was determined to be eligible for a Certificate of Exemption as reviewed by the Human Subjects Review Committee of the University of Washington, Seattle. Participation in the study was anonymous and without a request for any identifying information other than postal zip code and year of birth which were used to identify those women who erroneously filled out the questionnaires more than once. All women were asked to give consent prior to the first survey question.

Participants

Study participants were asked whether they had experienced any pregnancy-related hypertensive disorder, including preeclampsia (toxemia), HELLP syndrome, or pregnancy-induced hypertension (PIH) during any of their pregnancies. Participation was allowed for women who had their first pregnancy after 1990 and had not been pregnant in the past 3 months. The survey consisted of four web based questionnaires as well as an inquiry about current and past medical history including medication use, age, ethnicity, education level and characteristics of index and subsequent pregnancies (gestational age, birth weight, preeclampsia, HELLP syndrome or eclamptic seizures). Participants were requested to ask a friend or acquaintance of approximately the same age that had a normotensive pregnancy during the same year of the participant's hypertensive pregnancy to complete the survey as a control subject. Women with current or past neurological conditions or women who lived in a country where English is not the first language were excluded.

Questionnaires

The Cognitive Failures Questionnaire (CFQ)
The CFQ is a validated questionnaire and contains 25 items scored on a five-point scale.[17,18] It assesses how often over the past 6 months errors were committed in daily tasks of everyday life. In this study we used 18 of the 25 questions. The answers to 7 questions could not be accessed from the anonymous collection tool. The loss of data weakens the power of the tool but is not expected to create a bias between case and control groups. From the 18 questions we derived a total score ranging from 0 to 72. Higher scores on the CFQ indicate more cognitive failures.

The World Health Organization Quality of Life BREF (WHOQOL-BREF) US version
The WHOQOL-BREF is a validated abbreviated version of the WHOQOL-100 that contains 100 items developed to assess generic quality of life.[19] The WHOQOL-BREF contains 26 questions in four domains: physical health, psychological, social relationships and environment. Items can be scored on a five-point scale. Higher scores indicate higher quality of life. The mean score of items within each domain is used to calculate the domain score, ranging from four to 20. The first two questions are general questions that do not pertain to one of the domains but are examined separately: question one pertains to overall perception of quality of life and question two pertains to overall perception of health.

The Social Functioning Questionnaire (SFQ)
The Social Functioning Questionnaire (SFQ) is a validated questionnaire that contains eight items covering the following domains: work, household tasks, financial matters, family relationships, sexual relationships, social contacts, and spare time activities.[20] Items are

Figure 1. Overview of included participants

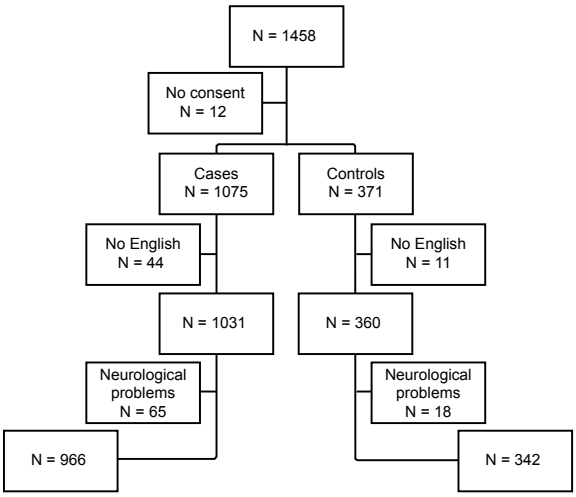


Table 1. General characteristics of cases and controls

		Cases (*n* = 966)	Controls (*n* = 342)	*p*-value
Age (years)		34 (19-60)	34 (20-57)	0.21
Education level	Less than high school	2 (0.2%)	0 (0%)	0.75
	High school	165 (17%)	53 (16%)	
	College/university	545 (58%)	199 (56%)	
	Doctorate/graduate school	254 (26%)	90 (26%)	
Ethnicity	Caucasian	868 (90%)	315 (92%)	< 0.05
	Hispanic/Latino	35 (4%)	5 (1%)	
	African American	22 (2%)	2 (1%)	
	Other	41 (4%)	20 (6%)	
Time since 1st pregnancy (years)		4 (0-20)	5 (0-20)	< 0.001
Number of pregnancies	1	510 (53%)	133 (39%)	< 0.001
	2	323 (33%)	123 (36%)	
	3	99 (10%)	58 (17%)	
	> 3	34 (4%)	28 (8%)	
Eclamptic seizures		58 (6%)		
Current psychiatric problems		168 (17%)	30 (9%)	< 0.001
Past psychiatric problems		324 (34%)	75 (22%)	< 0.001
History of migraine		389 (40%)	107 (31%)	< 0.01
Antihypertensive medication		172 (18%)	4 (1%)	< 0.001
PTSD		393 (41%)	43 (13%)	< 0.001

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

scored on a four point-scale, from which a total score can be derived with a range of 0–24. Higher scores indicate poorer social functioning. A score ≥ 10 is used as a cut-off point for poor social functioning.

The Breslau Short Screening Scale for Posttraumatic Stress Disorder (PTSD)
The Short Screening Scale for DSM-IV PTSD consists of seven items; five avoidance and numbing items and two hyperarousal items, scored 0 (no symptoms) or 1 (symptoms).[21] A cut-off ≥ 4 was used to indicate a greater likelihood of PTSD. Results of this PTSD screening scale are used in the regression analysis to determine the effect of pregnancy-related PTSD on the other questionnaires.

Statistical analyses

Statistical analysis was performed using Predictive Analytics Software Statistics version 18 for Windows (PASW Inc., Chicago IL, USA). All data were checked for normalcy of distribution using Shapiro–Wilk test and Levene's test for homogeneity of variance. Demographic and pregnancy characteristics, the prevalence of past or current psychiatric problems and use of antihypertensive medication were analyzed using chi-square test. Single imputation was used to replace missing values (< 5% of total data) in the questionnaires using estimated means per group. The group variable was coded as 0 vs. 1. Statistical analysis to compare the total scores of the questionnaires and the individual CFQ questions between groups was done using Mann–Whitney U test. Individual questions of the CFQ and question one and two of the WHOQOL-BREF were analyzed using chi-square test as well. Spearman's rho was used to assess correlations between the questionnaire scores. Univariable and multivariable linear regression with a forward stepwise inclusion was used to analyze the effects of group (cases vs. control), age, education level, elapsed time since first pregnancy, ethnicity, number of experienced pregnancies, eclamptic seizures, antihypertensive medication and history of migraines (a factor was selected for the multivariable analysis if $p < 0.25$ in the univariable regression, and the criterion for inclusion in the multivariable analysis was set at $p = 0.05$). Porcel et al. found a significantly higher prevalence of PTSD in the same group of women (43% vs. 14% in controls). (Porcel et al. personal communication) Therefore, we performed a second multivariable regression analysis combining PTSD with the aforementioned factors.

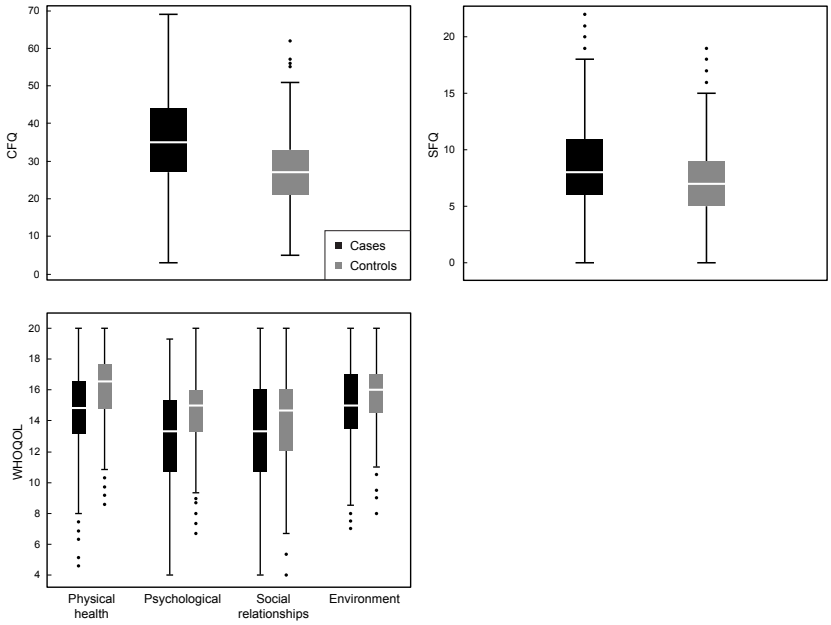
Results

Demographics

A total of 1458 women participated in the survey, of whom 1075 had some form of hypertensive disease during pregnancy (12% of Preeclampsia Foundation registrants).

Figure 1 depicts the number of excluded women plus the reasons for exclusion. Only participants from the USA, Australia, Great Britain, Canada and New Zealand were included. A total of 1308 participants were included for data analysis, including 966 cases, i.e. women who had some form of hypertensive disease during any of their pregnancies and 342 controls. i.e. parous women who had normotensive pregnancies. The self-reported

Figure 2. CFQ, SFQ and WHOQOL-BREF



For the CFQ and SFQ, higher scores indicate worse functioning. For the WHOQOL-BREF, higher scores indicate better functioning.

Table 2. Questionnaires: cases and controls

		Cases (*n* = 966)	Controls (*n* = 342)	*p*-value
CFQ	Total score 18 items	35 (3-66)	27 (5-62)	< 0.001
WHOQOL-BREF	Quality of life	4 (1-5)	4 (2-5)	< 0.001
	Satisfaction with health	3 (1-5)	4 (1-5)	< 0.001
	Physical health domain	15 (5-20)	17 (9-20)	< 0.001
	Psychological domain	13 (4-19)	15 (6-20)	< 0.001
	Social relationships domain	13 (4-20)	15 (4-20)	< 0.001
	Environment domain	15 (7-20)	16 (8-20)	< 0.001
SFQ		8 (0-22)	7 (0-19)	< 0.001

Results are expressed as median (min-max).

Table 3. Univariable and multivariable regression analysis

		Univariable		Multivariable	
Parameter		B	SE (B)	B	SE (B)
CFQ total (18 items)					
Group		8.16	0.72	7.49	0.71*
Age		-0.26	0.06	-0.17	0.06*
Eclampsia		6.00	1.60	3.28	1.51*
Migraine		4.32	0.69	3.50	0.64*
Education	College/university (reference)				
	Less than high school	10.04	8.37	4.41	7.91*
	High school	4.97	0.91	4.13	0.86*
	Doctorate/graduate school	-1.51	0.77	-1.35	0.73*
WHOQOL-BREF Physical health domain					
Group		-1.35	0.16	-1.12	0.16*
Antihypertensive medication		-1.22	0.21	-0.87	0.20*
Migraine		-0.99	0.14	-0.84	0.14*
Education	College/university (reference)				
	Less than high school	-1.19	1.79	-0.44	1.71*
	High school	-1.02	0.20	-0.72	0.19*
	Doctorate/graduate school	0.19	0.17	0.26	0.16*
WHOQOL-BREF Psychological domain					
Group		-1.63	0.17	-1.57	0.17*
Migraine		-0.67	0.16	-0.52	0.16*
Education	College/university (reference)				
	Less than high school	-0.41	1.99	0.09	1.92*
	High school	-0.96	0.22	-0.88	0.21*
	Doctorate/graduate school	0.25	0.18	0.28	0.18*
WHOQOL-BREF Social relationships domain					
Group		-0.99	0.21	-0.92	0.21*
Migraine		-0.79	0.19	-0.72	0.19*
WHOQOL-BREF Environment domain					
Group		-0.80	0.15	-0.74	0.15*
Age		0.04	0.01	0.02	0.01*
Migraine		-0.56	0.14	-0.48	0.13*
Education	College/university (reference)				
	Less than high school	-1.26	1.69	-0.76	1.66*
	High school	-0.68	0.18	-0.58	0.18*
	Doctorate/graduate school	0.37	0.16	0.35	0.15*

Univariable effects are shown only for factors included in the multivariable analyses. * $p < 0.05$.

Table 3. (continued)

		Univariable		Multivariable	
Parameter		B	SE (B)	B	SE (B)
SFQ total					
Group		1.56	0.25	1.45	0.24*
Migraine		1.09	0.22	0.94	0.22*
Education	College/university (reference)				
	Less than high school	1.89	2.78	1.37	2.72*
	High school	1.27	0.30	1.16	0.30*
	Doctorate/graduate school	-0.24	0.26	-0.28	0.25*

Univariable effects are shown only for factors included in the multivariable analyses. * $p < 0.05$.

prevalence of preeclampsia and/or HELLP syndrome among cases was 96.8% and 42 (3.2%) had gestational hypertension. Median age at the time of survey was 34 for both cases and controls. Median time since first pregnancy was 4 and 5 years respectively. Cases had significantly fewer pregnancies compared to controls. Fifty-eight cases (6%) reported having experienced eclampsia during one of their pregnancies. Cases more often reported: (1) current or past psychiatric problems requiring therapy, (2) a history of migraines and (3) use of antihypertensive medication. There was no difference in education level (Table 1).

Questionnaires

Cases scored significantly worse compared to controls on total scores and individual domain scores of all three questionnaires (Table 2 and Figure 2). This was also true for all the individual questions of the CFQ and question one and two of the WHOQOL-BREF: overall perception of quality of life and overall perception of health ($p < 0.001$). Results did not change when cases with PIH were excluded. On the SFQ, 385 (40%) cases and 73 (21%) controls scored ≥ 10, indicating poor social functioning. When the 924 cases with preeclampsia or HELLP were divided in early (< 34 weeks) versus late onset (> 34 weeks) preeclampsia, no significant differences were found for any of the questionnaires. The total CFQ score of 18 questions demonstrated good reliability (Cronbach's $\alpha = 0.91$), as did the SFQ total (Cronbach's $\alpha = 0.77$) and the WHOQOL-BREF domains (Cronbach's $\alpha = 0.82$, 0.85, 0.70 and 0.81 for physical health, psychological, social relationships and environment respectively).

Multivariable linear regression analysis

Table 3 shows the results of the multiple linear regression analyses incorporating group, age, education level, elapsed time since first pregnancy, ethnicity, number of experienced

pregnancies, eclamptic seizures, antihypertensive medication and history of migraines. The effect of group (cases vs. controls) remained significant on all outcomes (B 7.49 for CFQ, -1.12 WHO physical health, -1.57 for WHO psychological, -0.92 for WHO social relationships, -0.74 for WHO environment and 1.45 for SFQ). There was a significant effect of eclampsia on the CFQ (B 3.28), which decreased the effect of group from B 8.14 to 7.49. A history of migraines had a significant effect on all outcomes. Women using antihypertensive medication scored significantly worse only on the WHOQOL physical health domain. Elapsed time since first pregnancy did not have a significant effect on any of the outcomes, nor did the number of pregnancies. Incorporating PTSD in the analysis had a significant effect

Table 4. Multivariable regression analysis including PTSD

		Multivariable	
Parameter		B	SE (B)
CFQ total (18 items)			
Group		5.32	0.68*
PTSD		8.65	0.64*
Age		-0.15	0.05*
Migraine		2.73	0.60*
Education	College/university (reference)		
	Less than high school	9.63	7.40*
	High school	4.06	0.81*
	Doctorate/graduate school	-1.37	0.68*
WHOQOL-BREF Physical health domain			
Group		-0.59	0.15*
PTSD		-1.95	0.14*
Antihypertensive medication		-0.81	0.19*
Migraine		-0.65	0.13*
Education	College/university (reference)		
	Less than high school	-1.27	1.60*
	High school	-0.88	0.18*
	Doctorate/graduate school	0.26	0.15*
WHOQOL-BREF Psychological domain			
Group		-0.87	0.16*
PTSD		-2.60	0.15*
Education	College/university (reference)		
	Less than high school	-1.03	1.74*
	High school	-0.83	0.19*
	Doctorate/graduate school	0.28	0.16*

* $p < 0.05$.

Table 4. (continued)

		Multivariable	
Parameter		B	SE (B)
WHOQOL-BREF Social relationships domain			
PTSD		-2.26	0.19*
Migraine		-0.50	0.19*
WHOQOL-BREF Environment domain			
Group		-0.32	0.15*
PTSD		-1.52	0.14*
Migraine		-0.33	0.13*
Education	College/university (reference)		
	Less than high school	-1.61	1.59*
	High school	-0.58	0.17*
	Doctorate/graduate school	0.41	0.15*
SFQ total			
Group		0.55	0.23*
PTSD		3.22	0.22*
Migraine		0.60	0.21*
Education	College/university (reference)		
	Less than high school	2.71	2.52*
	High school	1.11	0.28*
	Doctorate/graduate school	-0.29	0.23*

* $p < 0.05$.

on all outcomes (Table 4). The significant effect of eclampsia on the CFQ disappeared and the effect of group (cases vs. controls) was less strong, but still significant on all outcomes except for the WHOQOL social relationships domain. There was no significant interaction between PTSD and group for any of the outcomes.

Discussion

Years following their pregnancy formerly preeclamptic women appear to perceive more cognitive problems, poorer quality of life and social functioning, including psychiatric problems requiring therapy, compared to a group of women with normotensive pregnancies. This difference remained significant after correction for age, early vs. late onset preeclampsia, education level, time since first pregnancy, ethnicity, number of pregnancies, eclamptic seizures, antihypertensive medication and history of migraines. A history of eclampsia did not change the effect of preeclampsia itself in the regression analysis. However, a history of eclampsia was associated with worse perceived cognitive

function whereas a history of migraine appears to have a significant effect on all outcomes. There are several possible explanations for our findings. A pregnancy complicated by preeclampsia may be experienced as traumatic and result in PTSD or depression.[13,22] These conditions may influence cognitive functioning, quality of life and social functioning in the long term. Indeed, we found a significant effect of PTSD on the questionnaires, which decreased the effect of preeclampsia. However, the effect of preeclampsia remained significant, suggesting that, in addition to psychological trauma, other factors also play a role. No differences were found for early vs. late onset preeclampsia, which suggests that the findings are not mediated by the effect of preterm birth and the stressors of caring for a premature child. We found that both preeclampsia and migraine independently influence self-reported cognitive functioning, quality of life and social functioning. Forty percent of cases and 31% of controls reported having migraine. The lifetime prevalence of migraine in women is 12–33%.[23] Our percentages may overestimate the true incidence of migraine in our cohort because we did not use a structured questionnaire to determine the diagnostic criteria of migraine. Preeclampsia and migraine seem related and seem to share a common pathway, involving vasodilatation, vascular dysfunction and platelet aggregation. Both have been associated with cardiovascular disease and brain white matter lesions.[1,8,24-27]

To our knowledge, there have been no previous studies with long-term follow-up in preeclampsia, and the main strength of our study is that we were able to reach a large number of women. Prior studies have evaluated cognitive functioning in formerly eclamptic women. Six to twenty four months after eclampsia, 18% of 123 interviewed women reported problems with concentrating, 14% had symptoms of mental depression.[3] Formerly eclamptic women scored significantly lower on the CFQ than normotensive parous controls, but no difference was found comparing previously preeclamptic women with controls.[2] In preeclampsia, small-scale studies evaluating objective neurocognitive functioning using a variety of tests have shown inconsistent results.[4-7]

A number of limitations of this study can be identified. An important issue is the potential for selection bias. About 12% of the Preeclampsia Foundation registrants responded to our call to participate in the study. Registrants with the Foundation are more likely Caucasian, higher educated, and more web connected. Our conclusions should be referenced to this group and generalized to others as deemed appropriate. In addition, it is plausible that women who experience the specific issues we investigated have a greater tendency to participate, which might overestimate the true scope. Also, only 342 controls responded to the preeclamptic women's request to participate in the study, which might skew the results into a more positive result.

Due to an unfortunate technical error, only the first 18 questions of the CFQ were available online. However, internal consistency and reliability (α = 0.91) were good and the lost questions were evenly divided over the three domains described by Rast et al.[17] Therefore, we consider our shorter CFQ version a valid indication of cognitive problems in our cohort. Another limitation is that we could not validate pregnancy data or diagnosis by

checking medical records due to the anonymity of this study, which may introduce recall bias. However, participating women likely seek out the Foundation due to adverse events associated with hypertension and were likely to have had some form of hypertensive disease in pregnancy. The diagnostic criteria for preeclampsia, eclampsia and HELLP syndrome are mentioned on the Foundation's website. In addition, if the case group contains women without hypertensive disease, this will bias exclusively toward the hypothesis. Since questionnaires elicit subjective answers, cognitive problems cannot be strictly defined. Lastly, the present study is descriptive. It is therefore not possible to draw firm conclusions on the causal relationship between preeclampsia and the outcomes of the questionnaires.

Our aim was to make an inventory of the nature and extent of long-term cognitive and psychosocial problems in formerly preeclamptic women. Although there is a potential for selection and recall bias, we feel our study emphasizes the need for further research in this field. Further study needs to focus on more accurately classifying the hypertensive categories and linking these to pregnancy outcomes. For example, perhaps women with a pregnancy loss or impaired infant have more significant cognitive dysfunctions. Moreover, women who had more than one pregnancy complicated by preeclampsia, whether or not they had a normal interval pregnancy, may have different recall of their symptoms. Our results would support the growing concern that preeclampsia cannot simply be considered a transient event. The subjective assessment of cognitive function, however, must be confirmed with objective neurocognitive testing. Further research should focus on the relationship between cardiovascular disease, migraine, brain white matter lesions and cognitive function.

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NEUROCOGNITIVE FUNCTIONING IN WOMEN WITH A HISTORY OF ECLAMPSIA: EXECUTIVE FUNCTIONING AND SUSTAINED ATTENTION

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4

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Abstract

Objective: Recently, information has emerged that formerly eclamptic women may suffer cognitive impairment. This may be related to cerebral white matter lesions. The few available reports demonstrate inconsistent results. We sought to elucidate cognitive performance after eclampsia in a pilot study.

Methods: Twenty-six eclamptic, 20 preeclamptic, and 18 healthy parous women performed the Sustained Attention to Response Task (SART; the ability to sustain mindful processing of repetitive stimuli that would otherwise lead to habituation) and the Random Number Generation Task (RNG; executive functioning, i.e., inhibition and updating/monitoring).

Results: Average age was 40 years, elapsed time since index pregnancy was 9 years. Education levels did not differ. There were no intercurrent illnesses. No significant differences were found on SART and RNG scores between groups.

Conclusions: This study was not able to demonstrate evidence for impaired sustained attention and executive functioning after eclampsia. Studies including a much wider range of neurocognitive tests amplified to posterior brain regions with larger groups are necessary.

Introduction

Eclampsia is an important complication of hypertensive disease during pregnancy. Cranial magnetic resonance imaging (MRI) within 24 hours following an eclamptic convulsion reveals vasogenic edema consistent with posterior reversible encephalopathy syndrome (PRES).[1,2] PRES is a dangerous clinicoradiological entity characterized by headaches, altered mental functioning, decreased alertness, visual disturbances, seizures, or coma.[3] Its pathophysiology is a matter of debate with current emphasis on failure of the autoregulatory capacity of the cerebral circulation in the presence of endothelial dysfunction and (often minimal) hypertension.[3,4] In this scheme, it is thought that subsequent hyperperfusion of the cerebral circulation may lead to disruption of the blood-brain barrier and formation of vasogenic edema that is believed to be reversible, at least initially. Recent doubts as to the complete reversibility of PRES in eclampsia have been raised. It now appears that not all formerly eclamptic women demonstrate complete reversibility of the white matter abnormalities seen on initial MRI.[2,5,6] Furthermore, formerly eclamptic women report cognitive dysfunction, specifically related to concentration, attention span, and memory.[7,8] These findings have challenged the paradigm that eclamptic women can expect full clinical recovery. Although formerly eclamptic patients report that their cognitive functioning is less efficient, it is unknown whether and to what extent this can be demonstrated objectively. Two small studies have been done in preeclamptic women so far, respectively 3 to 8 and 6 to 18 months postpartum, in which some cognitive impairment was seen on auditory-verbal memory, visual perceptional speed, and divided attention, but results were inconsistent.[9,10] No data are available about cognitive functioning in women who experienced eclampsia.

Cognitive functioning consists of different domains.[11] One of these domains and an important factor for daily human functioning is sustained attention, which reflects the capacity to maintain attentional activity over a longer period of time. Another domain pertains to executive functioning, which reflects the capacity to regulate behavior and control the contents of conscious thought. Problems that may arise due to impaired executive functioning are defective selfcontrol, emotional lability, irritability and excitability, impulsivity, rigidity, and attentional and behavioral difficulties. The subjective complaints of formerly eclamptic women seem to involve sustained attention and executive functioning, and therefore, neurocognitive tests suited to evaluate these functions were chosen. With this pilot study, we aimed to assess these two domains of cognitive functioning in formerly eclamptic women, more specifically, sustained attention and the executive functions of updating and inhibition involved in regulating the contents of the working memory.

Methods

Study population

The University Medical Center Groningen (UMCG) is an academic teaching and tertiary perinatal referral hospital in The Netherlands. A small percentage of healthy women with uncomplicated pregnancies choose to deliver in the UMCG as well. The population in the northern part of The Netherlands is predominantly Caucasian. Since 1988, an electronic admission, diagnosis, and delivery database has been kept up-to-date. From 1988 until 2005, 73 women were diagnosed with eclampsia. Eclampsia was defined as new onset of seizures after 20 weeks and within 1 week postpartum in women with preeclampsia. Preeclampsia was defined according to the standards of the International Society for the Study of Hypertension in Pregnancy.[12,13] Of these 73 women, the medical records were reviewed for accuracy of diagnosis of eclampsia. Upon reviewing the medical records, one formerly eclamptic participant was excluded because the diagnosis of eclampsia could not be confirmed. Two women died from cerebral complications (both due to hypoxic encephalopathy following severe cerebral edema) as a result of eclampsia, and one woman succumbed to cervical cancer several years after pregnancy. Exclusion criteria were epilepsy or other neurological or psychiatric disorders known to influence cognitive functioning, a history of alcohol or substance abuse requiring therapy, or pregnancy at the moment of testing. Each woman was matched for age and year of index pregnancy with one formerly preeclamptic woman and one healthy parous control. Matching took place before the invitations were sent. In total, 69 formerly eclamptic women were contacted, of whom 26 agreed to participate in this neurocognitive study. Eighteen healthy parous control women and 20 preeclamptic women were also willing to participate. Many non-participants in all groups mentioned the travel and time commitment as the reason for not being able to participate. Several formerly eclamptic women declined to participate due to fear of confrontation with their past illness and possible sequelae. All study participants were asked to complete a questionnaire related to current and past medical history and sociodemographic characteristics. The project was approved by the University Medical Center Groningen Institutional Review Board, and all women signed informed consent.

Sustained Attention to Response Task

The Sustained Attention to Response Task (SART) was used to measure the participant's sustained attention, which is defined as the ability to sustain mindful, conscious processing of stimuli of which the repetitive qualities would otherwise lead to habituation and distraction to other stimuli. This means that one has the capacity to maintain attention to an activity during a longer period of time. Performance on this brief and conceptually simple laboratory task is predictive of selfreported everyday attentional failures and

action slips in normal control participants.[14,15] The task consists of repetitive computer-administered visual stimuli in the form of digits ranging from 1 to 9. The participant has to press a key each time a digit appears, with exclusion of the digit 3. The digits follow each other in a rapid sequence (each digit appears for 250 milliseconds followed by an X presented for 900 milliseconds), with a total of 200 digits. Attention is required to withhold pressing when digit 3 appears. Several indices can be derived from SART performance: the number of omission errors (pressing the key when digit 3 appears), mean reaction time (RT) for correct responses (mean RT correct), pre-error RT (i.e., mean RTs of the four key presses prior to making an omission error), and a difference score calculated by subtracting pre-error RTs from mean RT correct. Note that higher difference scores are interpreted to be indicative of lapses in attention. That is, smaller pre-error RTs are relative to the usual time of responding (mean RT correct), indicating that the participant would be less engaged in consciously controlling her attentional resources and would be relying more on automatic responding.

Random Number Generation Task

The Random Number Generation (RNG) task was used to assess executive functioning. Two of those executive functions are response inhibition (the ability to inhibit strong automatic or dominant responses) and updating of working memory (the ability to monitor the relevance of incoming information and update and replace old information). Participants were instructed to say out loud numbers between and including 1 and 10 as randomly as possible. They were to provide a total of 100 numbers at a rate of one per second. The responses were entered into the RgCalc program (Lancaster, UK) to calculate various indices of randomness.[16] Two different factors concerning executive functions of working memory have been derived, namely the updating/monitoring component, reflecting the degree to which participants use each number to an equal extent (the ability to monitor and update

Table 1. Baseline characteristics

	Eclampsia (*n* = 26)	Preeclampsia (*n* = 20)	Controls (*n* = 18)	*p*-value
Age (y)	40 (6.3)	42 (6.3)	39 (7.4)	0.70
Elapsed time since index pregnancy (y)	9 (4.8)	10 (4.6)	9 (4.5)	0.83
Undergraduate/university education level (%)	9 (35%)	6 (32%)	6 (32%)	0.42
Nulliparous (%)	18 (69%)	12 (63%)	7 (37%)	0.08
EGA at delivery (wk)	33.0 (4.0)	34.0 (5.3)	39.6 (1.4)	< 0.0001
Birth weight (g)	1819 (882)	2038 (1314)	3536 (374)	< 0.0001

Results are expressed as mean or number; standard deviations and percentages are noted between parentheses. EGA = Estimated Gestational Age.

Table 2. Participants and non-participants

	Eclampsia participants (*n* = 26)	Eclampsia non-participants (*n* = 43)	Preeclampsia participants (*n* = 20)	Preeclampsia non-participants (*n* = 18)	Control participants (*n* = 18)	Control non-participants (*n* = 14)
Age (y)	40 (6.7)	38 (6.7)	40 (6.2)	39 (4.3)	40 (6.9)	37 (5.9)
Elapsed time since index pregnancy (y)	8 (5.1)	10 (7.4)	6 (4.5)	7 (4.2)	6 (4.8)	5 (2.6)
Birth weight (g)	1744 (948)	1699 (877)	2176 (1323)	2291 (1172)	3468 (527)	3537 (528)
EGA at delivery (wk)	33.2 (4.8)	32.6 (4.2)	34.5 (5.2)	35.3 (4.9)	40.0 (1.4)	39.7 (1.4)
Highest systolic blood pressure (mmHg)	194 (30)	194 (26)	181 (37)	173 (19)		
Highest diastolic blood pressure (mmHg)	113 (16)	117 (12)	101 (14)*	111 (11)*		
Multiple seizures (%)	13 (52%)	19 (42%)				

* $p = 0.04$ between formerly preeclamptic participants and non-participants. Results are expressed as mean or number; standard deviations and percentages are noted between parentheses. EGA = Estimated Gestational Age.

Table 3. Sustained Attention to Response Task results

	Eclampsia (*n* = 25)	Preeclampsia (*n* = 20)	Controls (*n* = 18)	*p*-value
Omission errors (n)	11 (5.1)	11 (6.3)	12 (6.0)	0.60
Mean RT correct (ms)	404 (50.1)	407 (58.6)	374 (58.6)	0.14
Pre-error RT (ms)	371 (40.5)	360 (47.9)	345 (43.7)	0.17
RT difference score (ms)	33 (29.9)	47 (39.9)	27 (30.4)	0.17

Results are expressed as mean; standard deviations are noted between parentheses. RT = Reaction Time.

Table 4. Sustained Attention to Response Task results for multiple seizures

	≥ 2 seizures (*n* = 12)	Controls (*n* = 18)	*p*-value
Omission errors (n)	13 (5.2)	12 (6.0)	0.87
Mean RT correct (ms)	382 (45.8)	374 (58.6)	0.71
Pre-error RT (ms)	362 (37.6)	345 (43.7)	0.29
RT difference score (ms)	20 (25.5)	27 (30.4)	0.54

Results are expressed as mean; standard deviations are noted between parentheses. RT = Reaction Time.

working memory), and the inhibition component (the ability to inhibit strong prepotent responses such as counting).[17,18] The updating/monitoring component consists of (1) mean repetition gap, the mean of the distances between two same numbers; (2) redundancy, the extent to which each number was selected with equal frequency; and (3) coupon, the mean number of responses before all the response alternatives from 1 to 10 were given. The inhibition component consists of (1) RNG, the frequency with which a particular number followed another number; (2) runs, the variance in length of successive ascending sequences of numbers; (3) combined adjacency, percentage of particular response pairs; and (4) turning point index, the number of responses that mark changes from ascending to descending sequences.[16,18] The updating/monitoring and inhibition components were calculated as follows: first, the relevant indices were recoded such that higher scores indicated better performance for all indices. Second, these indices were transformed into z-scores and summed for each component. Cronbach's α was 0.84 for the inhibition and 0.83 for the updating/monitoring scores, indicating good internal consistency.

Statistics

Baseline characteristics were compared using the χ^2 test, Kruskal-Wallis test, or one-way analysis of variance (ANOVA) where appropriate. One-way ANOVA was used to analyze the difference in the scores on the RNG and SART between the three groups; post hoc analysis (Student's t-test) was done to look at differences more extensively. Outliers were truncated to a value of one unit higher/lower than the second highest/lowest score.[19] The RNG and SART tests do not provide specific cutoff levels for normal or pathological states. Outcome data are therefore relative with regard to the other participants.[14-16] All tests were two-tailed with α set at 0.05.

Results

Baseline characteristics of the three groups were similar, except for gestational age at delivery and birth weight, as expected (Table 1). The population in the northern part of The Netherlands is predominantly Caucasian, as were all women who participated in this study. When comparing formerly eclamptic women who participated (n = 26) with those who declined to participate (n = 43), no significant differences were found in age, elapsed time since index pregnancy, birth weight, and gestational age at delivery. There were also no significant differences in number of single versus multiple seizures and highest systolic and diastolic blood pressures. In the formerly preeclamptic and control group, participants and non-participants also had similar characteristics (Table 2).

Table 5. Sustained Attention to Response Task results for single and multiple seizures

	1 seizure (*n* = 9)	≥ 2 seizures (*n* = 12)	*p*-value
Omission errors (n)	9 (3.8)	13 (5.2)	0.06
Mean RT correct (ms)	432 (35.6)	382 (45.8)	0.01
Pre-error RT (ms)	386 (31.8)	362 (37.6)	0.13
RT difference score (ms)	45 (26.5)	20 (25.5)	0.04

Results are expressed as mean; standard deviations are noted between parentheses. RT = Reaction Time.

Table 6. Random Number Generation task results

	Eclampsia (*n* = 26)	Preeclampsia (*n* = 19)	Controls (*n* = 18)	*p*-value
Inhibition	-0.199 (2.78)	-0.458 (4.26)	0.771 (2.88)	0.49
Updating/monitoring	0.644 (1.59)	0.135 (1.77)	-0.151 (1.87)	0.31

Results are expressed as mean; standard deviations are noted between parentheses.

Table 7. Random Number Generation task for multiple seizures

	≥ 2 seizures (*n* = 13)	Controls (*n* = 18)	*p*-value
Inhibition	-0.041 (2.28)	0.771 (2.88)	0.47
Updating/monitoring	0.504 (1.88)	-0.151 (1.87)	0.36

Results are expressed as mean; standard deviations are noted between parentheses.

Table 8. Random Number Generation task for single and multiple seizures

	1 seizure (*n* = 9)	≥ 2 seizures (*n* = 13)	*p*-value
Inhibition	-0.659 (3.64)	-0.041 (2.28)	0.60
Updating/monitoring	0.817 (1.45)	0.504 (1.88)	0.68

Results are expressed as mean; standard deviations are noted between parentheses.

Sustained Attention to Response Task

The frequency of omission errors (pressing the key when the digit 3 appears) did not differ between the groups, nor did the mean RT correct, the pre-error RT, and the difference score derived from the mean RT correct and pre-error RT. Thus, at group analysis, no difference was found comparing the three groups (Table 3). Formerly eclamptic women tended to be slower than controls. However, the difference was not statistically significant. To further explore performance in the formerly eclamptic group, specifically, the influence of multiple seizures, the subgroup of women who had more than one seizure was compared

with controls. However, no significant differences were found (Table 4). Comparing single seizures with multiple seizures, the multiple seizure group had a significantly shorter RT than the single seizure group, very similar to the control group (Table 5). The decrease in RT prior to an error in the multiple seizures group is smaller than in the single seizure group and in the other groups, which means that they do not accelerate as much prior to making an error.

Random Number Generation

For RNG inhibition and updating/monitoring scores, no significant difference was found between the three groups (Table 6). Individual group analysis did not reveal any differences either. Comparing RNG inhibition and updating/monitoring scores of controls with the subgroup of those formerly eclamptic women who had multiple seizures and comparing single seizures with multiple seizures also failed to show statistically significant differences (Table 7, Table 8).

Discussion

This pilot study was not able to demonstrate evidence for impairment on elements of the working memory, specifically the RNG and SART tasks for sustained attention and executive functioning, in formerly eclamptic women on a group level, nor in women who experienced multiple seizures. Because one would anticipate the control group to achieve the best score, we do not give much credibility to the found differences on the SART mean RT and decrease in RT prior to an error between the single and multiple seizures group.

Information about whether women who have experienced eclampsia can expect problems with their neurocognitive functioning is important. Several such women demonstrate cerebral white matter lesions on MRI weeks to years later.[2,5,6] In the general elderly population, cerebral white matter lesions have been associated with a decline in cognitive functioning and dementia.[20,21] Sustained attention, also known as vigilance, refers to the capacity to maintain an attentional activity over a period of time. It involves the frontal areas of the brain. RNG measures executive functioning, in which prefrontal and parietal areas of the brain are involved.

In a recent pilot study, formerly preeclamptic women underwent neuropsychological testing 3 to 7 months after delivery and scored significantly lower on most indices of the auditory-verbal memory tasks compared with controls.[10] In addition, considerably fewer words were learned and less recall was demonstrated after interference. In this study, no differences were found between formerly preeclamptic women and controls concerning tests for attention/concentration and executive functioning. Unfortunately, the sample size of that study was very small (n = 10) and did not include formerly eclamptic women. Recently, Baecke et al. showed that formerly preeclamptic women were impaired on the

WAIS III digit symbol coding task and the Paced Auditory Serial Addition Test for divided attention. These women, however, also reported more posttraumatic stress symptoms, and after analysis with posttraumatic stress score as a covariate, the differences on the tests disappeared.[9] Because of the inconsistent results in small groups, it is too early to accept the preliminary findings of these pilot studies as a valid reflection of the neurocognitive performance in formerly eclamptic women. A difference between the aforementioned studies and the study now performed is the interval between pregnancy and the moment of testing, which was 3 to 6 months and 6 to 18 months respectively in the other studies and was 3 to 19 years postpartum in this study.

The SART and RNG, both frontal lobe tasks, were specifically chosen to study the possible neurocognitive consequences of formerly eclamptic women, considering these women report complaints of attention and concentration problems.[8] However, persistent brain lesions in formerly eclamptic women appear to predominantly occur in the posterior parietal areas of the brain.[2,5,6] It might be that the perceived cognitive dysfunction of these women is incongruent with the actual brain lesions. Impairment on several other functions might be perceived by such women as attention and concentration problems. Alternatively, the presence, severity, and localization of brain white matter lesions in the group of formerly eclamptic women might be heterogeneous, making it difficult to detect neurocognitive impairment specifically related to certain brain regions.

When interpreting our data, there are several possible explanations for the lack of difference between formerly eclamptic women and controls. Obviously, the lack of difference may be real, which means that formerly eclamptic women do not demonstrate a problem with executive functioning and sustained attention. It may also be very possible that our study population was too small to detect any differences on the RNG and SART scores and hence a type II statistical error was introduced. However, even though the number of patients in this study may appear limited, in the context of the rare incidence of eclampsia it represents a sizeable study of which the results are clinically important. As was mentioned before, several formerly eclamptic women declined to participate because of fear of confrontation with the, often traumatic, experience of eclampsia. Therefore, some severe cases might have been missed in this study, which means that significant bias could have been introduced.

In conclusion, this pilot study was unable to demonstrate impaired sustained attention and executive functioning, important components of the working memory, in formerly eclamptic women. However, due to the aforementioned limitations of this study, specifically the introduction of a type II error and selection bias, it is not justified to extrapolate these results to formerly eclamptic women in general. Sample size calculation demonstrated that at least 50 to 100 women in each group are necessary to be able to demonstrate a possible significant difference on the individual components of the tests (using a difference of 1 for the RNG outcomes and 3 for the SART omission errors), which is currently not feasible due to the rare occurrence of eclampsia. Further studies into

the cognitive consequences of PRES in eclampsia are necessary and should concentrate on neurocognitive tasks of the posterior parietal parts of the brain. Additionally, it is interesting to include a group of women who have never been pregnant to elucidate a possible effect of pregnancy and motherhood on subsequent neurocognitive functioning in and of itself. To further elucidate neurocognitive functioning of formerly eclamptic women, studies incorporating larger groups of affected women and controls are needed, using a much wider range of different neurocognitive tests, specifically amplified to the posterior location of the brain lesions.

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NEUROCOGNITIVE FUNCTIONING FOLLOWING PREECLAMPSIA AND ECLAMPSIA; A LONG-TERM FOLLOW-UP STUDY

American Journal of Obstetrics & Gynecology

In press

5

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Abstract

Objective: Women who suffered preeclampsia and eclampsia may report subjective cognitive difficulties in daily life, the interpretation of which is cumbersome, since 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.

Methods: 46 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 (CFQ) and anxiety/depression by the Hospital Anxiety and Depression Scale (HADS).

Results: Both preeclamptic and eclamptic women performed worse on the motor functions domain ($p < 0.05$), without differences on the other domains. They scored worse on the CFQ ($p < 0.01$), the HADS anxiety ($p < 0.01$), and depression ($p < 0.05$) scales.

Conclusions: Women who suffered eclampsia and/or preeclampsia demonstrate no objective cognitive impairment as compared to 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.

Introduction

Women who suffered preeclampsia and/or eclampsia report cognitive problems years following 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, since they are also strongly influenced by non-cognitive factors, such as symptoms of anxiety and depression.[5,6] Preeclamptic women may exhibit such psychopathology following 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 following 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]

Since longer follow-up of neurocognitive performance is lacking, we aimed to study cognitive functioning in a relatively large group of women who suffered 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 to preeclamptic women, and that both groups would perform worse than controls. Since 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 (e.g. visual functioning tasks) as well as the frontal brain areas (e.g. attention and executive functioning).

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 before 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 neurosurgical 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. 1 control was excluded because she had professional knowledge of the neurocognitive tasks. 46 eclamptic women, 51 preeclamptic women and 48 controls remained available for analysis.

Age and level of education were similar in the three groups (Table 1). Education

Table 1. Overview of participant characteristics

		Eclampsia (*n* = 46)	Preeclampsia (*n* = 51)	Controls (*n* = 48)	*p*-value
Age (y)		39 (6.5)	39 (6.7)	40 (7.3)	0.56
Caucasian		44 (96%)	51 (100%)	46 (96%)	0.40
Elapsed time since index pregnancy (y)		8 (2-20)	6 (1-18)	6 (1-27)	0.02
Birth weight (grams)		1310 (300-4440)	1960 (310-4470)	3600 (2210-4620)	< 0.01
EGA at delivery (wk)		32 (22-42^{+1})	34+4 (26^{+2}-41)	40 (36^{+2}-40^{+2})	< 0.01
SGA < 10th percentile		14 (30%)	20 (39%)	4 (8%)	< 0.01
Early-onset (pre)eclampsia < 34 wk		28 (61%)	24 (47%)		
Nulliparous at index pregnancy		40 (87%)	34 (67%)	21 (44%)	< 0.01
Level of education	*Average*	18 (39%)	24 (47%)	18 (38%)	0.59
	High	28 (61%)	27 (54%)	30 (63%)	
DART IQ		99 (11.1)	98 (10.7)	99 (10.5)	0.87
Antidepressants (n)		0 (0%)	6 (12%)	2 (4%)	0.99

Results are expressed as mean (SD), median (min-max) or number (percentage). EGA = Estimated gestational age, SGA = Small for gestational age, DART = Dutch Adult Reading Test.

level was categorized according to the system of Verhage as described by Bouma in 2012 (1 being the lowest (less than primary school), and 7 the highest (academic degree, such as bachelor/master)).[19] None of the women were in the low education group (category 1 en 2). Average was defined as category 3-5 and 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 DART could not be administered. Another participant was unable to complete the DART due to dyslexia. The population in the northern part of the Netherlands is predominantly Caucasian, 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 cut-off 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?"

Neuropsychological tests (objective measures of cognitive functioning)

Participants completed a battery of 16 standardized, reliable and valid neuropsychological tests divided into 6 cognitive domains.[19,24] These tests are sensitive to cognitive impairment and have been validated in different populations (normal subjects, neurological and psychiatric patients) using different methods (e.g. correlational and factor-analytic studies as well as neuroimaging studies). Each cognitive domain consisted of verbal and non-verbal tasks. Tests were administered in a fixed sequence according to standardized instructions for each measure by two 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 non-dominant hand and the Trail Making Test part 5 (Motor Speed; Delis-Kaplan Executive Function System (D-KEFS)).[29]

Working memory (WM)

Visuospatial 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 non-verbal 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 (LTM)

Visuospatial 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 five 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 which entails 14 items scored on a 4-point scale (0-3).[36] Items were divided into two 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, USA). 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 due to an outlier were accepted. For measures (Trail Making Test) that were not-normally distributed, logarithmic transformation was employed. There were no differences in outcomes between these transformations and non-parametric tests. Patient characteristics were analyzed using Kruskall-Wallis test for non-normally distributed data and χ^2 test for categorical data. Antidepressant use was analyzed using Fisher's exact test comparing both patient groups to controls. Single imputation was used to replace two missing values in the questionnaire (due to a missed question) and two missing values (due to 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 One-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 contrast (which compares a level to the mean of subsequent levels, i.e. 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 to 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 in order to estimate the strength of significant effects between groups.[37] An effect size of partial $\eta^2 = 0.01$ was defined as small, $\eta^2 = 0.06$ as medium and $\eta^2 = 0.14$ as large.[37] In order to detect a medium effect size of $\eta^2 = 0.06$ on the multivariate analysis of the test domains for 3 groups, with a power of 0.80 and α of 0.05, 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

Table 2. Questionnaires

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	< 0.001
Forgetfulness	16 (5.8)	18 (6.1)	13 (4.1)	8.37	0.104	< 0.001
Distractibility	14 (5.8)	15 (5.8)	12 (3.6)	4.34	0.059	0.01
False triggering	12 (5.2)	13 (5.0)	9 (3.9)	7.40	0.095	< 0.001
Hospital anxiety and depression scale (HADS)						
Total score	12 (6.6)	11 (5.8)	8 (5.5)	6.20	0.081	< 0.005
Anxiety	7 (3.8)	6 (3.4)	5 (3.1)	6.08	0.077	< 0.005
Depression	5 (3.5)	4 (3.4)	3 (2.9)	3.87	0.054	0.02

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

(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 $p < 0.05$.

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, birth weight 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 to the preeclamptic group and controls. Since women with early-onset (pre)eclampsia did not show different results compared to women with late-onset (pre)eclampsia, results for this subgroup are not separately discussed.

Cognitive failures questionnaire (subjective cognitive functioning)

When comparing the three 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 ($p < 0.01$), but not between preeclamptic and eclamptic women. The effect size statistics indicate moderate effects. As shown in Figure 1, significantly more preeclamptic and eclamptic women compared to controls scored a considerable number of cognitive failures; 24 (52%), 35 (69%) and 8 (17%) respectively ($p < 0.001$). Cronbach's α 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.

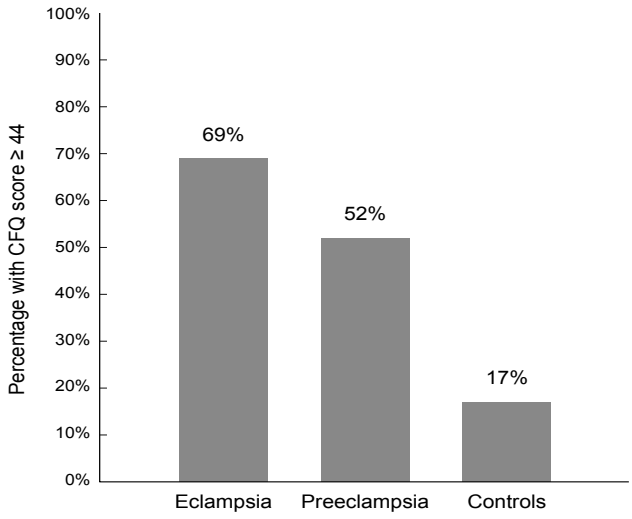
Anxiety and depression

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 to controls ($p < 0.01$). The effect size statistics indicate moderate effects. Cronbach's α was 0.81 for the HADS Anxiety subscale and 0.80 for the Depression subscale. Anxiety and depression subscales were strongly correlated (0.62).

Neuropsychological tests

Multivariate analysis of neuropsychological test domains only revealed a significant result for motor functions ($p < 0.05$) (Table 3) due to a significant difference in visuomotor speed measured by the Trail Making Test part 5 (D-KEFS) ($p < 0.001$). 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 ($p < 0.05$) and that both patient groups scored worse compared to controls ($p < 0.01$).

Figure 1. Percentage of participants with cognitive failures



Percentage of formerly preeclamptic and eclamptic women and controls with high Cognitive Failures Questionnaire (CFQ) score (cut-off value of 44). $\chi^2(2, N = 145) = 27.8$, $p < 0.001$.

Table 3. Multivariate analysis of cognitive domains of neurocognitive tests

Cognitive domain	Function	Test	Measure	Eclampsia (*n* = 46)	Preeclampsia (*n* = 51)	Controls (*n* = 48)	F(2, 142)	*p*-value	Effect size (partial η^2)
Visual perception							0.72*	0.70	0.025
	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							2.53*	0.02	0.051
	Visuomotor speed	Grooved Pegboard	Score dominant hand (time)	66 (10.1)	66 (9.2)	64 (8.5)	0.45	0.64	
			Score non-dominant hand (time)	74 (9.8)	73 (12.0)	72 (12.5)	0.11	0.89	
		Trail Making Test (D-KEFS)	Part 5: Motor Speed (time)	26 (1.5)	22 (1.3)	20 (1.3)	7.22	< 0.001	
Working memory (WM)							0.73*	0.63	0.015
	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)			

Results are expressed as mean (SD). Time is in seconds. * Multivariate analysis of variance (MANOVA) test statistics of between-group effect.

Table 3. (continued)

Cognitive domain	Function	Test	Measure	Eclampsia (n = 46)	Preeclampsia (n = 51)	Controls (n = 48)	F(2, 142)	p-value	Effect size (partial η^2)
Long-term memory (LTM)							1.08*	0.37	0.015
	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							0.54*	0.77	0.012
	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)			
Executive functioning							0.024	0.69*	0.73
	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. * Multivariate analysis of variance (MANOVA) test statistics of between-group effect.

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 ($p < 0.05$ 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 ($\beta = -0.22$, $p < 0.01$), Trail Making Test part 1 ($\beta = 0.21$, $p = 0.01$), Grooved Pegboard score non-dominant hand ($\beta = 0.20$, $p = 0.02$), Dutch Incomplete Figures Test ($\beta = 0.22$, $p = 0.02$), Stroop Color-Word Test part 2 ($\beta = 0.17$, $p = 0.04$) and part 3 ($\beta = 0.24$, $p = 0.003$) and the Tower Test ($\beta = 0.18$, $p = 0.06$). HADS total score was associated with the Corsi Block-Tapping Test ($\beta = -0,17$, $p = 0.04$), Dutch Incomplete Figures Test ($\beta = -0.29$, $p = 0.003$), Tower Test ($\beta = -0.27$, $p = 0.004$) and the WAIS-III Letter-Number Sequencing Test ($\beta = -0.23$, $p = 0.006$). Group (controls vs. preeclampsia and eclampsia) was not significantly associated with any of the tests, meaning that women with preeclampsia scored similar to controls, but for the Trail Making Test part 5 ($\beta = 0.26$, $p = 0.001$), as was shown previously in the multivariate analyses (MANOVA).

Discussion

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 to controls. Preeclamptic as well as eclamptic women reported significantly more cognitive failures in daily life and scored significantly higher for anxiety and depression, factors which 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 to 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 to controls. In the literature, executive functioning, or the control of complex, goal-directed behavior is the cognitive ability, which is most susceptible to 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 to 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 suffered (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 prior to 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 (HPA) axis resulting in increased cortisol levels and concomitant changes in cellular immunity, associated with hypertension and endothelial dysfunction.[48]

Alternatively, women who suffered eclampsia or preeclampsia more often demonstrate cerebral white matter lesions on long-term follow-up MRI compared to parous control women.[10,11] One could expect that the presence of such lesions may influence both subjective and objective cognitive functioning. However, non-obstetric 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 pre-pregnancy 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 which may have given rise to selection bias. However, most non-participating women could not be contacted because of change of address and/or phone number. Other non-participating 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 which 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 (i.e. 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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CEREBRAL WHITE MATTER LESIONS AND PERCEIVED COGNITIVE DYSFUNCTION: THE ROLE OF PREGNANCY

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7

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Abstract

Objective: Women who suffered eclampsia or preterm preeclampsia are twice as likely to demonstrate cerebral white matter lesions (WML) on MRI compared to age-matched women who had normotensive pregnancies, and they report more cognitive dysfunctions in everyday life. We aimed to determine whether pregnancy in and of itself has a relationship with the presence of WML and subjective cognitive dysfunction.

Methods: 81 parous women who had a normotensive pregnancy were matched for age with 65 nulliparous women and all underwent cerebral MRI. Presence of cerebral WML was rated and blood pressure was measured. Subjective cognitive functioning was assessed using the Cognitive Failures Questionnaire (CFQ).

Results: There was no difference in the presence (22% vs. 19%) of WML between parous and nulliparous women. Age was a predictor for the presence of WML, whereas the presence of current hypertension was not. Average CFQ score was not different between both groups, nor related to WML.

Conclusions: A history of pregnancy in and of itself is not related to the presence of cerebral WML and the perception of cognitive dysfunction. Because of the relationship with preterm preeclampsia and eclampsia, future research should focus on the clinical importance and development throughout the years of such cerebral WML in young women and focus on risk factors for cardiovascular disease.

Introduction

With the aging population, diseases such as dementia and stroke will become major health issues in the near future. A feature of such conditions is that preclinical structural cerebral changes, such as white matter lesions (WML) may be present years before clinically recognizable disease. The presence of such WML may be an important risk marker for the development of cognitive impairment, vascular dementia, Alzheimer's disease and stroke.[1-4] In individuals in their 50s and 60s WML are especially seen in combination with risk factors for small vessel disease such as hypertension and diabetes.[3-5]

White matter lesions are a frequent neuroimaging finding in elderly individuals, but their prevalence as well as their relationship with cognitive dysfunction in younger asymptomatic populations is unknown.[6] The prevalence of WML and perceived cognitive dysfunction in women who experienced (pre)eclampsia has recently been investigated by our group.[7-11] Women who suffered (pre)eclampsia report cognitive problems years following the index pregnancy, which appear to be related to memory, concentration and vision-related tasks of everyday life.[9-11] In addition, women who suffered eclampsia, or preterm preeclampsia (< 37 weeks), appeared twice as likely to demonstrate WML compared to age-matched women who had normotensive pregnancies.[7,8] The relationship between WML and perceived cognitive dysfunction in women who suffered preeclampsia/eclampsia is the focus of our ongoing work. While a direct causal relationship remains to be elucidated, we hypothesize that an underlying predisposition for vascular disease contributed to both the development of (pre)eclampsia as well as WML. However, in our previous studies, we found that one in five women who experienced a normotensive pregnancy also had WML at an average age of 37. This raises the question whether pregnancy and parity in and of itself have a relationship with the presence of such lesions and the perception of cognitive difficulties.

Therefore, the aim of this study was to compare the prevalence of cerebral WML in women who had normotensive pregnancies compared to nulliparous women and to determine the relationship with self-perceived cognitive dysfunction.

Methods

Participants

Participants who had a normotensive pregnancy formed the control group in follow-up studies assessing cerebral long-term consequences of preeclampsia. Recruitment and selection criteria have been published previously.[7-9,12] This project was approved by the University Medical Center Groningen Institutional Review Board and all women signed informed consent.

75 parous controls from our previous studies underwent MR imaging and six additional parous controls were included, leaving 81 controls for analysis. Nulliparous women were recruited between March 2012 and June 2013 by means of an invitation in local newspapers, on the Internet and among hospital personnel. Nulliparous women willing to participate were matched for age (± 2 years) and level of education to one of the parous women. A total of 65 women out of 134 eligible nulliparous women who responded to the recruitment advertisement could be matched and did not have MRI contraindications. 20 parous women did not complete the cognitive failures questionnaire (CFQ), (n = 60).

Women were excluded if they had MRI contraindications, neurological disorders such as epilepsy, demyelinating disorders, a known cerebrovascular accident, intracranial infections or a history of any intracranial surgery or were currently pregnant. Nulliparous women were excluded if they had experienced a pregnancy of more than 12 weeks duration, or if they had recent contact with a hospital concerning fertility treatment or diagnostic procedures.

All patients completed a short questionnaire about their current and past medical health. At the time of imaging, weight and blood pressure (manually, using an aneroid sphygmomanometer) were measured. Current hypertension was defined as a blood pressure of ≥ 140/90 mmHg and/or current antihypertensive medication use.

MRI protocol

Participants were invited to the 3-T MRI facilities (Philips Intera; Philips Medical Systems, Best, the Netherlands) of the Neuro-Imaging Center of the School for Behavioural and Cognitive Neurosciences in Groningen. The MRI protocol has been previously published by our group.[7,8] An experienced neuroradiologist rated the prevalence, size and number of WML and other structural brain abnormalities. WML were considered to be present if

Table 1. Overview of participant characteristics

	Parous women (n = 81)	Nulliparous women (n = 65)	p-value
Age (total range 21-59) (y)	37 (6.9)	37 (7.9)	0.81
Caucasian ethnicity	75 (93%)	63 (97%)	0.25
Weight (kg)	72 (10.8)*	73 (17.3)	0.59
Current hypertension	8 (10%)**	8 (13%)‡	0.60
Smoking	13 (16%)	8 (12%)	0.52
History of migraine	17 (21%)	15 (24%)	0.69
Elapsed time since index pregnancy (y)	6 (4.9)		
Primipara	40 (49)		

Results are expressed as mean (SD) or number (percentage). * n = 80, ** n = 78, ‡ n = 61.

hyperintense on fluid-attenuated inversion recovery (FLAIR), proton density-weighted and T2-weighted images and not as hypointense as liquor on T1-weighted images. A correction for inclusion of partial volume misclassification was made as described previously.[8]

Subjective cognitive functioning

The Cognitive Failures Questionnaire (CFQ) evaluates the number of errors committed in the completion of daily tasks.[13] 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 cut-off point for high CFQ total scores based on the Dutch population was set at 44, indicating cognitive problems.[14] The CFQ was developed as a valid self-report instrument to measure the tendency to make mistakes in everyday life.[13] In a healthy population, the CFQ is a valid measure of a stable cognitive resource that is involved in attention, memory and action in daily life, with good test-retest reliability for groups of individuals and good internal reliability.[15]

Statistical analysis

To achieve sufficient statistical power with α of 0.05 and β of 0.20, a total sample size of 150 women was needed to detect a difference in prevalence of WML of 20% (one-sided test), based on the difference found in our previous studies in eclamptic/preeclamptic women (41/37%) as compared to controls (21%).[7,8] In addition, with α of 0.05 and β of 0.20, we estimated that a total sample size of 100 women was needed to detect a difference in CFQ score (one-sided test) of 7 with a standard deviation of 14.[9] Statistical analysis was performed using IBM SPSS Statistics for Windows version 20 (IBM Corp., Chicago IL, USA). All data were checked for normality of distribution using Shapiro-Wilk test and Levene's test for homogeneity of variance. Demographic data were compared using χ^2 test for categorical data or Student's *t*-test for normally distributed data. The presence of WML was compared between groups using χ^2 test. CFQ total score was analyzed using Student's *t*-test, χ^2 test was used for cut-off scores. Univariate and multivariate regression analyses were used to identify possible determinants related to the presence of WML (binary logistic regression) and CFQ score (linear regression), i.e. age, current hypertension, migraine, smoking and weight. A determinant was selected for the multivariate analysis if $p < 0.25$ in the univariate regression.

Results

Participants

In total, 81 parous and 65 nulliparous women with an average age of 37 years underwent cranial MR imaging. Groups were not significantly different as to weight, current hypertension and smoking (Table 1).

White matter lesions

WML were present in 18 (22%) parous and 12 (19%) nulliparous women (p = 0.58). Small lesions were present in 10 (12%) parous and 10 (15%) nulliparous women (p = 0.61). Medium or large lesions were present in 11 (14%) parous and in 7 (11%) nulliparous women (p = 0.60). Presence of WML within the parous group was not different between women who experienced one (8; 20%) vs. multiple pregnancies (10; 24%) (p = 0.64). Univariate regression analysis revealed that age, OR 1.07 (1.01-1.13) p = 0.03, was a significant predictor for the presence of WML. Figure 1 shows the distribution of WML according to age in parous and nulliparous women.

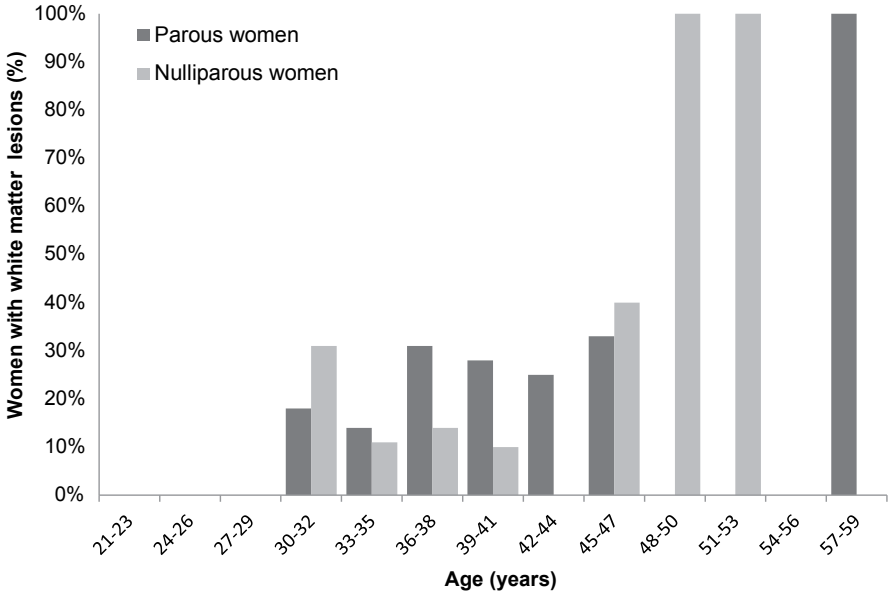
Subjective cognitive functioning

125 women (60 parous and 65 nulliparous women) completed the CFQ. There was no significant difference in CFQ total score between the groups (36 ± 11.0 for parous women and 33 ± 9.6 for nulliparous women, p = 0.16). No difference was found in the percentage of women scoring higher than the cut-off score of 44 (indicating cognitive problems): 11 (18%) parous women and 8 (12%) nulliparous women, p = 0.35. The presence of WML was not related to subjective cognitive function (CFQ score 34 ± 7.5 for women with WML and 35 ± 10.9 for women without WML), p = 0.77. Subjective cognitive function was not significantly different within the parous group between women who experienced one vs. multiple pregnancies (CFQ score of 36 ± 11.2 and 35 ± 11.1, respectively), p = 0.75. Univariate regression analysis revealed that none of the determinants in the equation were a significant predictor for CFQ scores.

Discussion

This study demonstrates that approximately one in five women in a population-based cohort with an average age of 37 has WML independent of pregnancy in and of itself. Furthermore, this study confirms that the prevalence of WML is associated with increasing age. Neither the prevalence of WML in this age category nor a history of pregnancy on average 6 years prior had any relationship with perceived cognitive failures in daily life.

Figure 1. White matter lesions and age distribution



Percentage of white matter lesions according to age in parous and nulliparous women.

Previous studies demonstrated brain WML twice as often in formerly eclamptic women and women with preterm preeclampsia compared to women following normotensive pregnancies.[7,8] An increased propensity for vascular disease in women with a history of preeclampsia may be an associated factor in the development of such lesions even though their pathogenesis has not become clear to date.[16] The present study shows that the presence of WML seems independent of pregnancy and parity.

The prevalence of WML in one-fifth of participants in this study with an average age of 37 years (range 21-59 years) is remarkable. Many studies have reported a high prevalence of WML in the elderly from 22.7% up to 100% in individuals aged 60 and over.[1,6,17-23] Few studies have been performed in younger cohorts; the reported prevalence at < 40 years of age is 0.5%-32%.[19,24-29] Differences in prevalence in the abovementioned studies might be due to different MRI field strengths and scanning sequences, different methods of WML rating, presence or absence of cardiovascular risk factors and differences in age range. For instance, two studies that found lower prevalence rates excluded patients with cardiovascular risk factors.[20,29] Higher prevalence in females compared to males has been reported in some, but not all studies.[5,6,23,29,30] The present study showed that WML presence was related to increasing age (OR 1.06), which is comparable to the OR found in the study of Chowdhurrey et al.,[20] however lower than in some other studies[21,29], which may be due to inclusion of different age ranges. The present study failed to show a significant effect of blood pressure on the presence of WML, while this relationship has been often described

in the literature as well as in prior studies of our own group.[8,31,32] This might be due to the relatively young and healthy population in the cohort now reported and, subsequently, the small number of women with hypertension, which is similar to the prevalence in the general Dutch population.[33] In this study we found no effect of parity on WML presence. Parity seems associated to cardiovascular disease in later life,[34] however, this association may be due to socioeconomic variables and may only hold true for women with ≥ 4 pregnancies, which were not present in our study.

The clinical implications of WML in young women are only speculative so far and are subject of further investigation. In the elderly, WML are related to cognitive decline and dementia.[35] Although perceived cognitive failures in formerly eclamptic and preeclamptic women have been previously reported,[9,10,36] minor neurocognitive impairment was found on neurocognitive tests.[37-39]

Up to several months postpartum, women frequently report cognitive deficits which are clustered under the terms 'mommy brain' or 'maternal amnesia'.[40] Postpartum women indeed show a small, but significant, impairment on some measures of cognition that place relatively high demands on executive cognitive control.[40] The animal literature views cognitive changes occurring during pregnancy and postpartum from an adaptive perspective. Rather than being a negative consequence of pregnancy, these cognitive changes may be seen as cognitive reorganization based on structural changes in the form of neuronal plasticity, in which social cognition which is relevant to maternal or fetal wellbeing is enhanced to the cost of other cognitive tasks.[40] In humans, fMRI studies investigating the parental response to infants show increased gray matter volumes in large regions of the prefrontal cortex, parietal lobe, and midbrain suggesting similar neuronal plasticity in humans.[41,42] Prenatal hormone levels seem to play a role in these changes.[43]

While such adaptations have not been assessed longitudinally, one could expect these postpartum cognitive changes to have subsided 6 years following pregnancy and indeed, we did not find significant differences in CFQ scores between parous and nulliparous women. In this study we found no effect of parity on CFQ scores. Glynn et al. found that adverse effects of pregnancy on memory function are compounded with successive pregnancies.[44] However, these measurements were only performed during gestation and at 3 months postpartum, but not more than 1 year postpartum.

To our knowledge, this is the first study to assess the long-term relationship between pregnancy and WML as well as subjective cognitive function. Moreover, it is one of the few studies in the literature to date to report on the relationship of WML and subjective cognitive dysfunction in such a young cohort in general. There are some methodological limitations to this study; no imaging data of the parous participants are available prior to their index pregnancy. Whether WML were present prior to pregnancy is therefore unknown. Second, determinants related to cardiovascular disease other than included in this study may play a role, such as blood glucose, family history, physical activity and hyperlipidemia. Even though the current study employed a state of the art 3-Tesla MRI scanner, we cannot

exclude that pregnancy does induce long-term structural brain changes. If so, such changes likely develop on a micro level and below a threshold for detection by the current state of the art neuroimaging techniques.

The examination of WML and their possible neurocognitive sequelae in younger individuals is important for a variety of reasons. It may help to understand the pathogenesis of such lesions and identify potentially modifiable factors in the early stages of their development. Moreover, since the presence of neuropsychiatric syndromes like Alzheimer, vascular dementia and depression has been related to WML the functional consequences of these lesions in mid-life are of utmost interest.[1,3,4,31] This age group should therefore be the focus of further work to identify risk and protective (modifiable) factors as it may prove to be the age at which preventive strategies need to be introduced to have an optimal impact on brain health in the future.

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SUMMARY, GENERAL DISCUSSION, CONCLUSIONS AND FUTURE PERSPECTIVES

Preeclampsia is the leading cause of maternal morbidity and mortality worldwide and may have implications for future health in a substantial number of young women. In the past decade, focus has shifted from the paradigm that preeclampsia is a disease from which pregnant women could expect full recovery, towards preeclampsia as a risk marker for future cardiovascular and cerebrovascular events.[3] With the aging population, cerebrovascular disease will become a major health issue in the near future. Although unraveling the consequences of preeclampsia for the maternal brain remains challenging, in this thesis some important insight is gained towards understanding future brain health in women who suffered preeclampsia and eclampsia.

Summary

Chapter 1 gives a general introduction to the maternal brain in (pre)eclampsia. Preeclampsia is a hypertensive, multisystem disorder of pregnancy, and a leading cause of maternal and fetal/neonatal morbidity and mortality. The central nervous system can be involved during the course of preeclampsia in the form of hyperreflexia, headaches, visual disturbances, mental status changes, eclampsia and in the most severe cases intracranial haemorrhage. Preeclampsia is an endothelial cell disorder characterised by poor placentation resulting in release of substances by the placenta, which enter the maternal circulation. Eclampsia is defined as the occurrence of tonic-clonic convulsions in a woman with preeclampsia and is considered a form of the Posterior Reversible Encephalopathy Syndrome (PRES). With PRES a combination of endothelial dysfunction and an increase in blood pressure is thought to result in failure of autoregulation of cerebral blood flow, with hyperperfusion and consequently vasogenic edema. Neuroimaging studies (MRI), carried out several years after (pre)eclampsia, may reveal hyperintense signals, so called cerebral white matter lesions (WML). WML in the general population and preeclampsia are associated with similar risk factors such as chronic hypertension, obesity, metabolic syndrome and insulin resistance and women with preeclampsia have higher risk of cardiovascular events and stroke later in life. In addition, both on short and long-term follow-up of formerly eclamptic women, self-reported memory complaints and symptoms of depression and anxiety have been described. These findings provided the fundament for this thesis.

Chapter 2 provides a review of the literature concerning potential long-term consequences of the Posterior Reversible Encephalopathy Syndrome (PRES) in eclampsia and non-obstetric patients. Although the encountered literature mainly consisted of case-studies, and long-term sequelae of PRES have been ill-described, some general conclusions can be made. In brief, eclampsia-related PRES has been associated less often with long-term neuroimaging abnormalities as well as cognitive problems, epilepsy or visual impairment as compared to non-obstetric PRES-related conditions. The main determinant for long-term problems in the non-obstetric population with PRES may be the underlying condition rather than

the PRES episode itself. Most reports suggest that late diagnosis or inadequate therapy of PRES may negatively influence the course of this syndrome. Although evidence-based therapeutic and long-term monitoring strategies are lacking to date, attention should be paid to timely and adequate treatment and follow-up of PRES patients.

Chapter 3 presents an observational study regarding self-reported cognitive functioning following pregnancies complicated by preeclampsia and normotensive pregnancies. A web-based survey was conducted in 966 women with a history of preeclampsia and 342 parous controls. The survey included 1) self-reported cognitive failures in daily life (short version (18 items) of the Cognitive Failures Questionnaire, CFQ), 2) social functioning (Social Functioning Questionnaire, SFQ) and 3) quality of life (abbreviated WHO Quality Of Life Questionnaire, WHOQOL-BREF). Women with a history of preeclampsia reported cognitive failures significantly more often as compared to controls (median CFQ score 35 and 27 respectively). In addition, they reported worse quality of life on the WHOQOL-BREF domains physical health (median 15 and 17), psychological health (median 13 and 15), social relationships (median 13 and 15) and environment (median 15 and 16), as well as more problems with social functioning (median SFQ score 8 and 7). Posttraumatic stress symptoms were found to account for part, but not all of this difference between preeclamptic women and controls. Although the study may have encountered selection and recall bias and the difference in scores appear modest, women with a history of preeclampsia perceive more cognitive and social problems, and report poorer quality of life compared to women who had normotensive pregnancies.

In **chapters 4 and 5**, objective cognitive functioning in formerly eclamptic and preeclamptic women was evaluated using a battery of neurocognitive tests. **Chapter 4** describes a pilot study assessing executive functioning (specifically inhibition and updating/monitoring) and sustained attention (the ability to sustain mindful processing of repetitive stimuli that would otherwise lead to habituation) several years following a eclamptic or preeclamptic pregnancy. 26 eclamptic women, 20 preeclamptic women and 18 controls who had a normotensive pregnancy performed the Sustained Attention to Response Task (SART) and the Random Number Generation (RNG) task. No significant differences were found on SART and RNG scores between groups, nor in women who experienced multiple seizures suggesting that there was no influence of severity of eclampsia. **Chapter 5** subsequently describes a larger study conducted in formerly preeclamptic and eclamptic women several years following the index pregnancy, encompassing an extensive range of 6 neurocognitive domains using sensitive, standardized neurocognitive tests: visual perception, motor function, working memory, long-term memory, attention and executive functioning. In addition, anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) and subjective cognitive functioning was measured by the CFQ. 46 eclamptic, 51 preeclamptic and 48 control women who had normotensive pregnancies completed

the neurocognitive test battery, the 25-item CFQ, and the HADS. Formerly eclamptic and preeclamptic women demonstrate no objective cognitive impairment in a test setting, aside from slighty lower visuomotor speed, as compared to controls (Trail Making Test part 5: 26, 22 and 20 seconds respectively). They did report more cognitive failures (average CFQ score of 43, 47 and 36 respectively) and more symptoms of anxiety and depression (average HADS score of 12, 11, and 8 respectively) as compared to controls, but no difference between eclamptic and preeclamptic women was found. Concluding, even though women who suffered eclampsia or preeclampsia do report more cognitive failures in daily life, in a well-structured test setting they do not demonstrate clear cognitive impairment. The reported cognitive failures (CFQ) by formerly preeclamptic and eclamptic women had a strong association with symptoms of anxiety and depression. The CFQ may be interpreted as a measure of executive control of behavior, in which individuals with symptoms of anxiety and depression experience cognitive failures mainly in complex and stressful daily life events. In this scheme it is hypothesized that high levels of stress hormones may be detrimental for executive control and increase susceptibility for experiencing cognitive failures.

Chapter 6 describes the relationship between cerebral white matter lesions (WML) found on MRI, subjective and objective measures of cognitive functioning and self-reported symptoms of anxiety and depression. Objective neurocognitive test results and questionnaires pertaining to subjective cognitive functioning and symptoms of anxiety and depression (**chapter 5**) were compared in women with and without WML on MRI. 41 eclamptic, 49 preeclamptic and 47 control women underwent both neurocognitive testing and MRI and completed the questionnaires. On average 6 years following the index pregnancy, women who suffered eclampsia or preterm preeclampsia (< 37 weeks) more often have WML (40%) as compared to women who had a normotensive pregnancy (21%). The presence of cerebral WML neither seem to bear a relationship with subjective or objective measures of cognitive functioning nor with symptoms of anxiety and depression in all groups. On the other hand the report of cognitive failures in these formerly preeclamptic and eclamptic women seems strongly related to the presence of symptoms of anxiety and depression. Complex and stressful situations, which require planning, may lead to cognitive failures in women who experience symptoms of anxiety. Because most associations between WML and cognitive impairment are found in the elderly, young women with an average age of 40 years may not (yet) suffer overt sequelae related to WML. Therefore, whether there may be development of cognitive impairment in later life in women who suffered eclampsia or preterm preeclampsia is currently unknown.

Since WML are also found in one fifth of women who had a normotensive pregnancy **chapter 7** describes the effect of pregnancy in and of itself on the prevalence of cerebral WML on MRI and subjective cognitive failures (CFQ). 81 women who had a normotensive pregnancy

were compared to 65 age-matched nulliparous women. Average age was 37 years in both groups and average elapsed time since pregnancy was 6 years. No difference was found in the prevalence of WML between parous and nulliparous women (prevalence of 22% vs. 19%). Parous and nulliparous women scored similar on the 25-item CFQ (average of 36 and 33). Only age was found to be a predictor for the prevalence of WML, whereas the presence of chronic hypertension was not. This may be due to the relatively young and healthy population in the cohort, and consequently, a low incidence of chronic hypertension. Whereas a high prevalence of WML (up to 100%) has been reported in individuals aged 60 and over, the few studies in younger cohorts (< 40 years of age) report a prevalence of 0.5%-32%, which is in the same range as the 20% described in this chapter. In short, 6 years later a history of pregnancy in and of itself does not seem to be related to the presence of WML and subjective cognitive problems.

General discussion

Following the summary of the studies presented in this thesis, a background will be provided against which eclampsia and preeclampsia can be seen as an important marker for future brain health. Subsequently, the results of this thesis will be discussed below and allow for a number of conclusions and future recommendations to be made.

The maternal brain in (pre)eclampsia

Preeclampsia is a disorder in which generalized endothelial dysfunction, altering the vascular reactivity, plays an important role.[1] The maternal brain can be involved in preeclampsia, characterized by hyperreflexia, headaches, visual disturbances, mental status changes, tonic-clonic convulsions (eclampsia) and, in the most severe cases, intracranial haemorrhage. Although the exact pathophysiology of eclampsia remains to be elucidated, it is generally thought that it develops in preeclamptic women when, in the presence of endothelial dysfunction, blood pressure exceeds the upper limit of cerebral autoregulation.[2] Evidence is increasing that the effects of a preeclamptic pregnancy for women's health may not be restricted to the pregnancy and early postpartum period, but represent a risk marker for future health.

Preeclampsia, cerebral small vessel disease and white matter lesions

In the past decade, research has revealed an association between preeclampsia and cerebrovascular and cardiovascular disease later in life, especially in women who suffered early-onset preeclampsia.[3] The incidence of cardiovascular disease such as stroke and ischaemic heart disease is higher following a preeclamptic pregnancy compared to women who had normotensive pregnancies.[3,4] Preeclampsia likely reveals a failure to adapt to the metabolic and vascular challenge of pregnancy. Pregnancy may therefore be a 'stress test' for later life health issues. It has been proposed that there is a shared constitutional risk for both the development of preeclampsia and cardiovascular disease in later life rather than a causal pathway between preeclampsia and cardiovascular disease.[5] Preeclamptic women have an unfavourable cardiovascular risk profile with higher fasting glucose levels, larger waste circumference and hypertension.[5] Although it is possible that much of the excess risk of future ischaemic heart disease and stroke is explained by the association of preeclampsia and chronic hypertension, preeclampsia itself appears to be an independent risk marker.[6]

Cardiovascular disease is one of the main causes of mortality in elderly females. The early identification of women with risk factors could possibly prevent future cardiovascular morbidity and mortality. Therefore, a history of preeclampsia has been added as a risk factor to the cardiovascular risk classification in women.[7] This increased cardiovascular

risk would render preeclamptic women eligible for lifestyle interventions and preventive therapy at lower thresholds.[7]

The prevalence of cerebral white matter lesions (WML) on MR imaging in formerly eclamptic women and women who suffered preterm preeclampsia is higher compared to controls who had a normotensive pregnancy (**chapter 6**).[8,9] WML prevalence was similar in eclamptic and preeclamptic women (**chapter 6**). The white matter of the cerebrum consists of nerve fibers (axons surrounded by a myelin sheath), neuroglial cells and vascular structures. In regions of white matter pathology, such as destruction of axons, cavitation or infarction, WML are seen as a high intensity signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI scans, revealing a high water content. In the elderly, postmortem studies demonstrate areas of WML showing a hypoxic response, arteriolar sclerosis, amyloid angiopathy and reduced endothelial vascular integrity which suggest chronic hypoperfusion.[10,11] WML are often divided into subcortical and periventricular WML. Subcortical WML mainly seem to disrupt intermediate corticocortical connections (association fibers), which have a high density in the white matter areas close to the gray matter.[12] Periventricular WML are thought to disrupt long connections from subcortical structures to cortical areas.

In older subjects WML are a frequent finding on MRI and, together with lacunar infarction and cerebral microbleeds, they are considered part of the continuum of neuroimaging features representing cerebral small vessel disease.[13] Cerebral small vessel disease, or cerebral microangiopathy, is a term used for a syndrome of clinical, cognitive and neuroimaging findings which are thought to arise from affected perforating arterioles, capillaries and venules resulting in insidious brain damage in the cerebral white and deep grey matter.[13] The mechanisms underlying cerebral small vessel disease are thought to be related to arteriolosclerosis, hypertension and early endothelial failure. The permeability of the cerebrovascular endothelium increases with age.[14] Cerebral small vessel disease develops over many years before it becomes clinically relevant but is the most common cause of vascular dementia and may also be seen in Alzheimer's disease.[15,16] Most available neuroimaging studies concerning WML are performed in the elderly. However, of 200 patients admitted for a TIA or stroke, who had cerebral small vessel disease, 31% was younger than 55 years. When cerebral small vessel disease (WML) is seen in younger individuals, vascular risk factors like hypertension and smoking likely play an important role.[17] It is suggested that some degree of cerebral small vessel disease is related to the normal process of aging while the presence of cardiovascular risk factors may accelerate this development.

In the past decade it has been hypothesized that the WML seen following a pregnancy complicated by eclampsia[8] may be a consequence of the cerebral edema in the posterior brain areas seen in the acute moment (PRES).[18] However, several findings in this thesis and previous studies now question a direct causal relationship between PRES and WML. First, as discussed in **chapter 2**, PRES in eclampsia has been associated less frequently with long-

term neuroimaging abnormalities such as infarction or haemorrhage than non-obstetric PRES-related conditions and the main determinant for the abnormalities following non-obstetric PRES-related conditions seems to be the underlying condition instead of the PRES episode in and of itself.[19] Second, since WML are found just as often in women who suffered preterm preeclampsia without seizures[9] it is less likely that there is a causal relationship between an episode of PRES (eclampsia) and the presence of WML several years later. Third, whereas brain edema in PRES is mainly located in the posterior areas, WML in formerly eclamptic and preeclamptic women as well as parous controls seem to be located mainly in the frontal areas of the brain (**chapter 6**).[20] Finally, as discussed in **chapter 7**, WML are also present in about one-fifth of women who had a normotensive pregnancy[8,9] as well as in one-fifth of nulliparous women of the same age category (average age of 37 years). All of the aforementioned arguments make a causal relationship between vasogenic edema in PRES and subsequent WML on follow-up less likely. However, an additive effect of the PRES episode in and of itself, specifically in cases who are confronted with cytotoxic edema, remains a possibility.

An alternative, more plausible, explanation for the pathogenesis of WML in women who suffered eclampsia and preterm preeclampsia and, to a lesser extent in women of childbearing age in general, may be that they are a part of the continuum of cerebral small vessel disease seen in the normal aging process, with an important additional role for cardiovascular risk factors. The latter may particularly be the case in women who suffered eclampsia and preterm preeclampsia, as the presence of WML in these women appears associated with the presence of chronic hypertension.[9] Especially women with preterm preeclampsia have an increased risk of hypertension, ischaemic and haemorrhagic stroke in later life.[4] Indeed, we found that mainly those women who suffered eclampsia and preterm preeclampsia more often have WML as compared to controls. The lack of a relationship between WML and chronic hypertension in women who had a normotensive pregnancy and nulliparous women (**chapter 7**) might be due to the relatively young and healthy population in the cohort now reported and, subsequently, the small number of women with chronic hypertension.

A history of migraine headaches has been associated with a higher incidence of hypertensive disorders during pregnancy, with odds-ratios ranging from 1.1 to 3.7.[21-34] In addition, migraine, just like preeclampsia, has been associated with a higher prevalence of cerebral white matter lesions and stroke.[35-38] Whether preeclampsia and migraine are independent determinants of cerebral WML remains to be elucidated.

Measures for subjective and objective cognitive functioning

Chapters 3 and 5 describe a substantial number of women reporting some degree of impaired cognitive, social and mental wellbeing years following (pre)eclampsia. The Cognitive Failures Questionnaire (CFQ) revealed subjective cognitive difficulties as compared to controls who

had a normotensive pregnancy. In **chapter 5**, there was no difference between eclamptic and preeclamptic women in subjective cognitive functioning, nor in symptoms of anxiety and depression. In **chapter 3** however, eclampsia seemed to have a small but significant additional effect on subjective cognitive functioning. These findings confirm what has been found in earlier studies reporting problems related to (prospective) memory, concentration, attention, indecisiveness, and vision-related tasks of everyday life.[39-42] Preeclamptic and eclamptic women did not reveal difficulties on objective measures of cognitive functioning (**chapters 4 and 5**). In general, there are some difficulties interpreting subjective as well as objective measures of cognitive functioning which will be now be outlined.

How can the Cognitive Failures Questionnaire be interpreted?

Two important aspects of the CFQ should be mentioned. First, the CFQ has been associated with emotional factors such as anxiety and depression. The CFQ can also be interpreted as a trait measure of adverse psychological reactions, such as anxiety, to complex stressful situations.[43,44] The direction of causality has not been clearly demonstrated. The CFQ appears to relate strongly to the view that individuals display in regard to their own worth/worries about one's cognition.[45,46] Second, more recently, the CFQ has also been associated with executive control of behavior. It may be viewed as a reflection of a person's experience of difficulties with executive functioning in everyday life (e.g. "Do you have trouble making up your mind?" and "Do you start doing one thing at home and get distracted into doing something else (unintentionally)?").[43] It may be difficult to capture these difficulties using a neurocognitive test battery in a laboratory environment. Executive functioning is represented by a higher level system which integrates several basic cognitive functions and surpass separate functions.[47] It directs and controls cognitive processes when faced with non-routine situations. Executive functioning is especially appealed to in new, complex and unknown situations, in which rapid and efficient adjustment of behavior to the environment is needed because routine solutions do not suffice. In a test setting, cognitive failures are more likely to occur by using standardized tasks in which cognitive processes such as planning, working memory, response inhibition and cognitive flexibility are required. However, even when a person functions well in a structured test setting, there may still be problems in novel and complex situations of everyday life. A standardized test setting is usually quiet with few distractions, there are clear instructions and time points for task initiation and completion, and the subject is asked to complete one task at a time. In contrast, in daily-life situations the individual needs to initiate, plan, organize and monitor his own behavior (e.g., self-initiation, self-organizing, self-monitoring and evaluating their purposeful behavior). Problems mainly occur in complex, unexpected and novel situations, which are usually unstructured and with numerous distractions, and require multitasking.[43,47,48] Interestingly, high levels of stress hormones have been linked to executive control[49] and thus symptoms of anxiety and depression may give rise to cognitive failures in complex and stressful daily-life events.

Expectations about cognitive failures may have caused women with a history of eclampsia or preeclampsia to overestimate the frequency of these failures and to attribute them to the experience of their complicated pregnancy. Indeed patients with pre-existing knowledge about a possible relationship of their medical condition and cognitive complaints report significantly more complaints than patients without this knowledge.[50] Whether this phenomenon is at play in women with a history of (pre)eclampsia is unclear. Knowledge concerning possible cognitive deficits following preeclampsia is not widespread in the general population, with very few studies performed so far.

Taken together, on the basis of these findings, we suggest that the everyday cognitive failures measured by the CFQ may be interpreted as difficulties in executive control of behavior, which manifest themselves primarily in unstructured, complex and stressful daily life events, which require a high level of executive functioning. **Chapters 4 and 5** did not reveal cognitive impairment on neurocognitive testing in a structured task setting in formerly eclamptic and preeclamptic women who report subjective cognitive failures. In addition, women who suffered eclampsia and preeclampsia have higher levels of stress (symptoms of anxiety and depression), which may be the result of stress as a trait as well as environmental stress factors (such as a preeclamptic pregnancy and preterm birth).

How can dissimilar results for subjective and objective cognitive functioning be reconciled?
While the CFQ did seem to be significantly correlated to objective neurocognitive functioning concerning the (sub)domains of visual perception, visuomotor speed, attention and executive functioning in this thesis (**chapter 5**), for most other domains this was not the case. Several studies concerning subjective and objective cognitive functioning have been performed in the non-obstetric domain, i.e. following brain injury, epilepsy, bipolar disorder, menopausal symptoms, Parkinson's disease, multiple sclerosis and cancer.[51] Similar findings (i.e. subjective cognitive problems without objective cognitive dysfunction) have been described as compared to the studies in this thesis. In patients with multiple sclerosis, subjective cognitive failures (CFQ) were not associated with neurocognitive functioning, and patients seem to underestimate their performance on neurocognitive tasks.[52] Patients with multiple sclerosis and mild cognitive complaints suffered more symptoms of anxiety, depression and mental fatigue.[53] Treatment of these factors did not influence scores on neurocognitive tests, but did improve subjective impairment.[54] Similar relationships have been described in women receiving breast cancer treatment; while subjective cognitive complaints partially reflected neurocognitive performance and were related to white matter integrity, they seemed to be multifactorial and related to emotional distress.[55-58] These similar findings in other, relatively young patient groups endorse our finding that subjective cognitive functioning is determined by other factors than solely objective cognitive functioning as measured in a test setting. In young individuals the CFQ is likely to mainly reflect executive control of behavior, in which symptoms of anxiety and depression contribute to the experience of cognitive failures in complex and stressful daily life events,

requiring executive functioning.

Another important consideration pertaining to the disparate results between subjective and objective cognitive functioning is related to the ecological validity of neurocognitive tests. The term ecological validity is used in reference to generalizability (the extent to which performance on a test will be predictive of daily life functioning) and representativeness (the extent to which a test corresponds to situations in daily life).[47] Development of neurocognitive tests over the years has diverged into several directions. While some tests were developed in order to correlate neurocognitive functioning with structural brain lesions seen on neuroimaging, others have focused mainly on evaluating everyday cognitive (dis)abilities with ecologically valid tests. Subtle cognitive complaints may not come to surface in a test setting, which is usually quiet with few distractions, with clear task initiation and completion, and a one-task-at-a-time programme.[47] This is in contrast to daily life behavior, which is usually unstructured with numerous distractions and requires flexibility, ability to plan, organize and monitor.

What is the relationship between subjective and objective cognitive functioning and cerebral white matter lesions (WML)?

In the elderly, measures of both objective and subjective cognitive functioning (CFQ) are associated with the presence of WML.[59,60] However, as elaborated in **chapter 6**, this does not seem to be the case in younger individuals. We studied whether WML in formerly eclamptic and preeclamptic women are associated with cognitive functioning. Several years following pregnancy, in women with an average age around 40, the presence of WML does not seem related to either subjective or objective cognitive functioning. It is quite possible that the topographical location of WML contributes to whether or not cognitive dysfunction comes to surface. White matter lesions in women who had eclampsia or preeclampsia are mainly located in the subcortical regions, while periventricular, and not subcortical WML, seem to be associated with cognitive impairment and dementia in the elderly.[61] Furthermore, in the elderly, subcortical WML seem mostly associated to depressive symptoms,[62] while in women with a history of eclampsia or preeclampsia, subcortical WML did not seem related to higher depression scores. While this seems reassuring, it cannot be excluded that WML in women who suffered eclampsia or preterm preeclampsia may start to demonstrate an impact in later life. The WML in these women are mainly located in the frontal brain areas (**chapter 6**), which are the areas involved in executive functioning in complex daily life situations. At younger age, these women may still be able to compensate for minor dysfunction, which may cost effort and contribute to fatigue. At older age, and increasing WML burden, compensatory mechanisms may no longer suffice. Indeed, not the mere presence, but rather the severity of WML may play a major role with regards to cognitive sequelae. With aging, the WML burden may increase and gray matter volume decrease, and the aging brain may have reduced ability to compensate for cognitive dysfunction.[63] It is possible that the detrimental effects of WML, and their associated risk factors such

as hypertension, have not come to surface in individuals in their 30-40's, and require longitudinal follow-up of ≥ 20 years. In this regard, limited research involving (epi)genetic features suggests possible parallels between preeclampsia and late-onset Alzheimer's disease for several loci. For example, genes located on 10q22, among which the *STOX1A* transcription factor, are expressed both in the placenta in preeclampsia and the brain in Alzheimer's disease and possibly regulate genes involved in cognitive decline.[64,65]

Emotional factors and subjective cognitive failures; cause or consequence?

In general, the association between subjective cognitive complaints and emotional aspects is quite complex with unclear direction of causality. As alluded to in the prior paragraph some major components deserve to be mentioned in light of this thesis. First, emotional and subjective cognitive complaints may both be a consequence of a common neurovascular pathogen such as cerebral structural abnormalities (e.g. WML).[59,62] However, while this has been demonstrated in the elderly population we were unable to demonstrate this in our younger cohort of women with a history of eclampsia or preeclampsia (**chapter 6**). Second, cognitive failures may not just be epiphenomena of symptomatology of anxiety and depression.[66] An explanation for the cognitive failures often seen with anxiety and depression is that they may be interpreted as a measure of executive control of behavior. Anxiety and depression may give rise to cognitive failures in complex and stressful daily-life events.[48] High levels of stress hormones seem detrimental for executive control and make a person susceptible for cognitive failures.[67]

Due to the cross-sectional nature of the measurements in this thesis, it is obviously not possible to draw firm conclusions about cause and effect relationships. It is possible that symptoms of anxiety and depression were already present prior to pregnancy. Both depression and anxiety in early pregnancy seem associated with the subsequent development of preeclampsia (odds-ratio of 2.5 and 3.2 respectively).[68] The experience of cognitive problems in daily life may have caused these women to enter a negative cycle revealing symptoms of anxiety and depression and vice versa. The precise biochemical mechanism behind this course of events remains speculative: distress conditions during pregnancy may lead to preeclampsia by increasing cortisol levels, which are associated with hypertension and endothelial dysfunction.[69] Alternatively, symptoms of anxiety and depression may come to surface following a (pre)eclamptic pregnancy. Indeed, and in accordance with earlier studies, this thesis reveals more symptoms of anxiety and depression in women with a history of (pre)eclampsia (**chapter 5**).[70-73] In this thesis no significant effect of preterm birth was found on subjective or objective neurocognitive test results, anxiety or depression (**chapter 5**).

In addition to anxiety and depression, women with a history of preeclampsia are at increased risk (OR = 3.48) for screening positive for Posttraumatic Stress Disorder (PTSD).[74] Women with eclampsia were at even higher risk (OR = 9.76). PTSD may develop following

a traumatic stressor such as threatening death or injury associated with helplessness or great fear. It is characterized by re-experiencing the trauma through intrusive memories, avoidance and a state of arousal. Indeed, a pregnancy complicated by preeclampsia might be a traumatic experience. These pregnancies are often associated with interventions, infant hospitalization and even perinatal mortality. Having a premature child is associated with negative job-related, relational, financial and social effects.[75] Moreover, preeclampsia and eclampsia can potentially be life threatening for both mother and fetus. PTSD has been related to cognitive deficits, even in the absence of comorbid conditions such as depression.[76] Self-reported complaints following PTSD pertain to concentration, attention, new learning and recall.[76] Indeed, PTSD score was positively related to the number of subjective cognitive failures in our study (**chapter 3**). Stramrood et al.[70] found a similar rate of PTSD in women with premature rupture of membranes, suggesting that the delivery itself is not necessarily the factor causing the traumatic experience but the trauma might rather be related to sudden hospitalization or neonatal complications.

Final conclusions

This thesis demonstrates that women who experienced a pregnancy complicated by eclampsia or preeclampsia experience more cognitive failures and symptoms of anxiety and depression several years following their pregnancy while neurocognitive testing did not reveal evidence for (sub)clinical cognitive dysfunction. Women with preterm preeclampsia and eclampsia more often have WML compared to women with a normotensive pregnancy and nulliparous women of the same age. Pregnancy in and of itself does not seem to play a role in the presence of WML. The presence of WML was not associated with neurocognitive test results, self-reported cognitive failures, or symptoms of anxiety and depression. Subjective cognitive failures are difficult to interpret and are probably multifactorial. Self-reported cognitive failures in the studies now described can be interpreted as a measure of executive control of behavior, in which symptoms of anxiety and depression, whether or not preexistent, may contribute to the development of cognitive failures mainly in complex and stressful daily-life events. The role of PTSD should not be underestimated, although not studied in this thesis. It cannot be ruled out that the WML and subjective cognitive complaints might be an indicator for development of cognitive dysfunction as women age.

The findings in this thesis support the transition in the obstetrical literature from the paradigm that preeclampsia is a condition from which women can expect full recovery, towards evidence that preeclampsia is an event occurring in the scheme of long-term emotional, cardiovascular and cerebrovascular health. Even though no objective cognitive impairment was demonstrated in our cohorts their report of subjective cognitive complaints deserve careful attention. We extrapolate that follow-up and timely intervention to restore emotional well-being may be important. In addition, offering more structure in planning, execution and monitoring of primary relevant tasks in daily life, and to explore its effect on subjective cognitive problems may be worthwhile. Considering the presence of WML and often chronic hypertension in women with a history of eclampsia or preterm preeclampsia, such women should be considered an important group for targeting early interventions to prevent later cardiovascular and cerebrovascular disease.

Future perspectives

Future research should mainly cover two pathways: (1) to determine the influence of intervention strategies for symptoms of anxiety and depression and subsequent self-reported cognitive difficulties and (2) long-term follow-up (i.e. 30-40 years) of preeclamptic women to determine the risk of development of cognitive decline at older age.

Intervention strategies for perceived cognitive dysfunction

Contemporary interventions are mainly aimed at elderly individuals who express subjective cognitive deficits but who lack objective cognitive impairment. Such interventions seem effective in reducing emotional reactions towards cognitive functioning.[77,78] Some elements of these programs may also be useful in younger individuals, such as negative stereotyping, personal goals and beliefs (an approach targeting knowledge, perception and beliefs about cognitive functioning) in addition to compensatory strategies. These interventions are not specifically aimed, however, at cognitive problems arising in complex and stressful situations.

Future studies in women with a history of (pre)eclampsia could aim at possible treatment strategies incorporating two different aspects which have to be attuned. First, treatment may focus on dysexecutive problems in daily life. This may consist of psycho-education in combination with providing women with an organized structure in daily life. Improved goal setting and planning skills may be obtained by gaining insight and awareness in ones limitations and development of effective compensatory strategies. Individuals may also be encouraged to effectively anticipate unexpected situations. Clinically relevant therapy should be multifaceted, since multiple aspects are needed for adequate executive functioning: self-awareness, concrete goal-setting, planning, selfinitiating, self-monitoring and evaluating, self-inhibiting, flexibility and problem solving and strategic behavior.[79] Such a multifaceted treatment program has proven to be successful in improving daily life executive functioning in individuals with acquired brain injury.[80] Second, as far as the symptoms of anxiety, depression and PTSD are concerned, treatment could focus on cognitive behavioral therapy or EMDR, which have been sparsely studied for PTSD following childbirth.[81-83] There may also be an additional role of debriefing and counselling, although there are inconsistencies regarding their therapeutic effect.[84] Finally, intervention studies should evaluate the effects on subjective cognitive outcome measures, symptoms of anxiety and depression, quality of life measurements as well as ecologically valid cognitive tests.

Preeclampsia and future risk of cognitive decline?

This thesis shows that several years following a pregnancy that was complicated by

eclampsia or preeclampsia, at an average age of 40 years, women show no clear cognitive impairment employing an extensive neurocognitive testing battery, but they do report considerable subjective cognitive dysfunction. These subjective cognitive problems should not be trivialized since it cannot be excluded that (subgroups of) these women may develop cognitive impairment when they are older. Longer follow-up studies of 20-30 years would provide insight whether there is a relationship between (pre)eclampsia and subjective cognitive difficulties earlier in life and cerebrovascular disease and overt cognitive decline later in life. Since cognitive decline is thought to be a result of a long-term processes taking place over at least 20-30 years[85], the importance of preventive strategies during adult life is emphasized. Since life expectancy continues to increase, the understanding of cognitive ageing will be one of the main challenges in the next decade.

Cerebrovascular disease and life style intervention

Women with a history of preeclampsia are at increased risk of developing cardiovascular or cerebrovascular disease in later life.[3,4] Midlife cardiovascular risk factors (such as obesity, hypertension and sedentary life style) are associated with an increased risk of cognitive impairment at 20 years follow-up (individuals ≥ 65 years).[86] Longtime exposure to elevated blood pressures or poor control of hypertension are particularly detrimental. Lifestyle interventions after preeclampsia are thought to reduce cardiovascular risk with about 4-13%.[6] Lifestyle intervention may therefore be an important focus for future studies evaluating prevention of the development or aggravation of white matter lesions in formerly eclamptic and preeclamptic women.

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NEDERLANDSE SAMENVATTING

Pre-eclampsie is een zwangerschapsgerelateerde aandoening en is wereldwijd één van de meest voorkomende oorzaken van maternale en foetale ziekte en sterfte. De aandoening wordt gekenmerkt door het ontstaan van hypertensie en proteïnurie tijdens de tweede helft van de zwangerschap bij een voorheen normotensieve vrouw. In Nederland komt pre-eclampsie voor bij ongeveer 3% van de zwangerschappen, maar in ontwikkelingslanden ligt het percentage een stuk hoger (rond de 15%). Pre-eclampsie is een systemische aandoening, waarbij gegeneraliseerde endotheeldysfunctie kan leiden tot de verstoring van de doorbloeding van verschillende organen, waaronder de hersenen (in de vorm van eclampsie). Eclampsie wordt gekenmerkt door het optreden van tonisch-clonische insulten bij een vrouw met pre-eclampsie. Andere neurologische verschijnselen zijn hyperreflexie, hoofdpijn, visusstoornissen, veranderingen in het bewustzijn, en in het meest ernstige geval intracerebrale bloedingen. Hoewel eclampsie weinig voorkomt in Nederland (tijdens 0,1% van de zwangerschappen), is het wel verantwoordelijk voor een substantieel deel van de maternale sterfte (3,5 per 100.000 levend geborenen).

Hoofdstuk 1 is een inleiding op dit proefschrift. Er wordt hier ingegaan op de veronderstelde pathofysiologie van eclampsie. Eclampsie wordt gezien als een uiting van het Posterior Reversible Encephalopathy Syndrome (PRES). PRES wordt beschreven als een reversibele, neurotoxische en neurometabole aandoening met een karakteristiek klinisch en radiologisch beeld. Neuroradiologische beeldvorming wordt gekenmerkt door hersenoedeem, voornamelijk in de witte en grijze stof van de pariëtaal- en occipitaalkwab. Bij eclampsie wordt verondersteld dat wanneer, in combinatie met endotheeldysfunctie, de bloeddruk boven de maximale grens van de autoregulatie stijgt er sprake is van geforceerde vasodilatatie. Hierdoor ontstaat hyperperfusie en beschadiging van de bloed-hersenbarrière en wordt er vasogeen oedeem gevormd. Vanwege de ernst van de klinische ziektebeelden en het hersenoedeem wordt wel gedacht dat PRES en eclampsie gevolgen kunnen hebben voor de maternale gezondheid op kortere en langere termijn. In **hoofdstuk 2** wordt de huidige literatuur over de langetermijngevolgen van PRES bij eclampsiepatiënten en bij niet-obstetrische patiënten samengevat en besproken. Eerder onderzoek liet zien dat er, jaren na de zwangerschap, meer wittestoflaesies in de hersenen worden gezien bij vrouwen na eclampsie en preterme pre-eclampsie. Waar eerst werd gedacht dat deze laesies een direct gevolg waren van het hersenoedeem ten tijde van het eclamptisch insult wordt nu meer een samenhang verondersteld met de aanleg voor hart- en vaatziekten bij deze vrouwen. Pre-eclampsie en wittestoflaesies zijn geassocieerd met vergelijkbare risicofactoren, zoals chronische hypertensie, obesitas, metabool syndroom en een verhoogd risico op cardiovasculaire en cerebrovasculaire aandoeningen op latere leeftijd. De betekenis van wittestoflaesies bij vrouwen na eclampsie en preterme pre-eclampsie is vooralsnog onbekend en in dit proefschrift wordt beoogd daar meer duidelijkheid in te brengen.

Naast de aanwezigheid van wittestoflaesies, rapporteren vrouwen die eclampsie doormaakten vaker subjectieve cognitieve problemen. In **hoofdstuk 3** wordt dit

geïnventariseerd door middel van een vragenlijst en in **hoofdstuk 4 en 5** wordt door middel van neurocognitieve testen onderzocht of er daadwerkelijk sprake is van cognitieve dysfunctie. Ook wordt de samenhang met emotionele factoren besproken. In **hoofdstuk 6** wordt de relatie tussen de aanwezigheid van wittestoflaesies en cognitief functioneren geanalyseerd. Tot slot wordt in **hoofdstuk 7** het voorkomen van witte stof laesies beschreven na het doormaken van een zwangerschap die niet gecompliceerd werd door preeclampsie of eclampsie.

In **hoofdstuk 2** wordt een literatuuroverzicht gegeven over de langetermijngevolgen van het Posterior Reversible Encephalopathy Syndrome (PRES) bij eclampsie en bij niet-obstetrische aandoeningen. De literatuur bestaat voornamelijk uit casestudies en slechts weinig is beschreven over mogelijke langetermijngevolgen. Een aantal algemene conclusies kunnen worden geformuleerd. PRES bij eclampsie lijkt minder vaak geassocieerd te worden met langetermijnafwijkingen bij neuroradiologische beeldvorming, cognitieve problemen en epilepsie, dan PRES bij niet-obstetrische aandoeningen. De belangrijkste determinant voor het ontstaan van deze langetermijnproblemen na PRES bij niet-obstetrische aandoeningen lijkt eerder de onderliggende aandoening te zijn, die vaak langere tijd bestaat. Dit in tegenstelling tot eclampsie, wat een "voorbijgaande" aandoening is. Daarnaast lijkt een niet-tijdige diagnose of inadequate behandeling van PRES een rol te spelen bij het al dan niet ontstaan van langetermijngevolgen. Hoewel er momenteel geen evidence-based therapie noch zinvolle follow-up strategie beschreven zijn, wordt in de literatuur het belang van tijdige en adequate behandeling en follow-up van PRES patiënten benadrukt.

Hoofdstuk 3 bespreekt de resultaten van een observationele studie over zelfgerapporteerd cognitief functioneren na een zwangerschap gecompliceerd door pre-eclampsie vergeleken met een normotensieve zwangerschap. 966 vrouwen die pre-eclampsie doormaakten en 342 controles die een normotensieve zwangerschap hadden, vulden een online vragenlijst in. Deze vragenlijst bestond uit 1) vragen over cognitieve problemen in het dagelijks leven (een verkorte versie van de *Cognitive Failures Questionnaire* met 18 items, CFQ), 2) vragen over sociaal functioneren (de *Social Functioning Questionnaire*, SFQ) en 3) vragen over kwaliteit van leven (de verkorte *WHO Quality of Life Questionnaire*, WHOQOL-BREF. Vrouwen die pre-eclampsie doormaakten rapporteerden significant meer cognitieve problemen dan controles (CFQ mediaanscore van 35 en 27). Tevens rapporteerden zij een slechtere kwaliteit van leven op de WHOQOL-BREF domeinen fysieke gezondheid (mediaanscore van 15 en 17), psychologische gezondheid (mediaanscore van 13 en 15) en sociale relaties (mediaanscore van 13 en 15) en omgeving (mediaanscore van 15 en 16) en ook scoorden zij slechter op sociaal functioneren (SFQ mediaanscore van 8 en 7). De aanwezigheid van posttraumatische stresssymptomen verklaarde gedeeltelijk, maar niet volledig, de slechtere score van vrouwen die pre-eclampsie doormaakten. Hoewel de kans bestaat dat er sprake is van selectiebias en recall bias en hoewel de gevonden verschillen

op de WHOQOL-BREF en SFQ in deze studie van matige grootte zijn, geven deze data een indicatie dat vrouwen die pre-eclampsie doormaakten vaker cognitieve en sociale problemen en een lagere kwaliteit van leven ervaren in het dagelijks leven dan vrouwen na een normotensieve zwangerschap.

In **hoofdstuk 4 en 5** is het cognitief functioneren van vrouwen die pre-eclampsie en/ of eclampsie doormaakten beoordeeld door middel van een neurocognitieve testbatterij. In hoofdstuk 4 wordt een pilotstudie beschreven waarin voornamelijk is gekeken naar executief functioneren (de sturing en controle over cognitieve processen, meer specifiek inhibitie en updating/monitoring) en volgehouden aandacht (de vaardigheid om de aandacht vast te houden bij de bewuste verwerking van herhaaldelijke stimuli die anders tot gewenning zouden leiden), meerdere jaren na het doormaken van een zwangerschap gecompliceerd door pre-eclampsie of eclampsie. 26 vrouwen met eclampsie, 20 vrouwen met pre-eclampsie en 18 controles met een normotensieve zwangerschap voerden de *Sustained Attention to Response Task* (SART) en de *Random Number Generation task* (RNG) uit. Er werden geen significante verschillen gevonden tussen de groepen en evenmin was er een duidelijk effect aantoonbaar van het aantal eclamptische insulten: vrouwen die meerdere eclamptische insulten doormaakten scoorden vergelijkbaar. In **hoofdstuk 5** wordt vervolgens een grotere studie beschreven, bij vrouwen die verscheidene jaren eerder pre-eclampsie of eclampsie doormaakten. Er werd gebruik gemaakt van een uitgebreide testbatterij met gevoelige en gestandaardiseerde neurocognitieve testen verdeeld over 6 domeinen. De domeinen bestonden uit visuele perceptie, motorisch functioneren, werkgeheugen, langetermijngeheugen, aandacht en executief functioneren. Daarnaast werden symptomen van angst en depressie gemeten door middel van de *Hospital Anxiety and Depression Scale* (HADS) en subjectieve cognitieve problemen werden gemeten aan de hand van de *Cognitive Failures Questionnaire* (CFQ). 46 vrouwen die eclampsie doormaakten, 51 vrouwen die pre-eclampsie doormaakten en 48 controles met een normotensieve zwangerschap voerden de neurocognitieve testen uit en vulden de 25-item CFQ en HADS in. Er werd geen neurocognitieve dysfunctie gezien in vrouwen die eclampsie of pre-eclampsie doormaakten vergeleken met controles, behalve een iets lagere visuomotorische snelheid (*Trail Making* Test deel 5: respectievelijk 26, 22 en 20 seconden). Ze rapporteerden echter wel meer subjectieve cognitieve problemen (gemiddelde CFQ score van respectievelijk 43, 47 en 36) en meer symptomen van angst en depressie (gemiddelde HADS score van respectievelijk 12, 11 en 8), waarbij er geen verschil bleek tussen vrouwen met eclampsie en pre-eclampsie. Concluderend rapporteren vrouwen die eclampsie of pre-eclampsie doormaakten wel meer subjectieve cognitieve problemen in het dagelijks leven, maar in een gestructureerde testsetting is er geen objectief aantoonbare cognitieve dysfunctie. De gerapporteerde subjectieve cognitieve problemen bleken sterk samen te hangen met symptomen van angst en depressie. Men kan de CFQ interpreteren als een maat voor executieve controle, waarbij individuen met symptomen van angst en depressie cognitieve

problemen ervaren, met name in complexe en stressvolle situaties in het dagelijks leven. Hoge stressniveaus zijn nadelig gebleken voor executieve controle en deze maken een individu gevoelig voor cognitieve misstappen.

In **hoofdstuk 6** wordt de relatie onderzocht tussen cerebrale wittestoflaesies, en subjectief en objectief cognitief functioneren en symptomen van angst en depressie. De resultaten van de testbatterij en vragenlijsten zoals beschreven in **hoofdstuk 5** bij vrouwen met en zonder wittestoflaesies (MRI) werden vergeleken. Van 41 vrouwen die eclampsie doormaakten, 49 vrouwen die pre-eclampsie doormaakten en 47 controles waren zowel neurocognitieve testresultaten als beeldvorming beschikbaar. De prevalentie van wittestoflaesies bij vrouwen die preterme (pre-)eclampsie doormaakten, is gemiddeld 6 jaar na de zwangerschap hoger (40%) dan bij controles (21%). Er waren geen duidelijke verschillen zichtbaar tussen vrouwen met pre-eclampsie en eclampsie. De aanwezigheid van deze wittestoflaesies hangt echter niet samen met subjectief of objectief cognitief functioneren, en ook niet met symptomen van angst en depressie. Er bleek wel een sterk verband te bestaan tussen zelfgerapporteerd cognitief dysfunctioneren in vrouwen die pre-eclampsie of eclampsie doormaakten en symptomen van angst en depressie. In aanwezigheid van deze symptomen kan, in geval van complexe en stressvolle situaties waarin een beroep wordt gedaan op het vermogen tot plannen, verminderd cognitief functioneren ervaren worden. De meeste associaties tussen wittestoflaesies en cognitieve dysfunctie zijn beschreven in oudere populaties. Het is mogelijk dat de relatief jonge vrouwen die meededen aan de studies uit dit proefschrift, met een gemiddelde leeftijd van 40 jaar, (nog) geen gevolgen van wittestoflaesies ondervinden. Toekomstig onderzoek moet aantonen of vrouwen die (pre-)eclampsie doormaakten op latere leeftijd alsnog meetbare cognitieve dysfunctie zullen ontwikkelen.

In **hoofdstuk 7** wordt het effect van het doormaken van een zwangerschap op zich op de aanwezigheid van wittestoflaesies en subjectieve cognitieve problemen beschreven, omdat wittestoflaesies ook worden gezien bij eenvijfde van de vrouwen die een normotensieve zwangerschap doormaakten. 81 vrouwen die een normotensieve zwangerschap doormaakten werden vergeleken met 65 nullipare vrouwen van vergelijkbare leeftijd. De gemiddelde leeftijd was 37 jaar in beide groepen en de verstreken tijd sinds de zwangerschap was 6 jaar. Het percentage vrouwen met wittestoflaesies verschilde niet tussen de twee groepen (prevalenties van respectievelijk 22% en 19%). Terwijl er een hoge prevalentie van wittestoflaesies (tot 100%) is beschreven bij ouderen boven de 60 jaar, laten de schaarse studies in individuen jonger dan 40 jaar een prevalentie zien van 0,5-32%, in overeenstemming met de in deze studie gevonden 20%. De groepen scoorden vergelijkbaar op de 25-item CFQ (met een gemiddelde score van 36 en 33). Alleen leeftijd bleek een voorspeller te zijn voor de aanwezigheid van wittestoflaesies, maar de aanwezigheid van chronische hypertensie was dat niet. Dit kan mogelijk veroorzaakt worden door de relatief

jonge en gezonde populatie in deze studie, en daardoor een lage incidentie van chronische hypertensie. Concluderend, het doormaken van een zwangerschap op zich lijkt geen rol te spelen in de aanwezigheid van wittestoflaesies en subjectieve cognitieve problemen, 6 jaar na dato.

Hoofdstuk 8 betreft een algemene discussie en conclusies. Dit proefschrift toont aan dat vrouwen die een zwangerschap doormaakten die gecompliceerd werd door eclampsie of pre-eclampsie jaren later vaker cognitieve problemen en symptomen van angst en depressie ervaren in het dagelijks leven terwijl er geen sprake is van objectief aantoonbare (sub)klinische cognitieve dysfunctie op neurocognitieve tests. Vrouwen die pre-eclampsie en eclampsie doormaakten hebben vaker neuroradiologisch aantoonbare wittestoflaesies dan vrouwen die een normotensieve zwangerschap doormaakten en nullipare vrouwen. Zwangerschap op zichzelf lijkt geen rol te spelen in de aanwezigheid van deze wittestoflaesies en de aanwezigheid van deze wittstoflaesies lijkt niet gerelateerd aan objectieve neurocognitieve testresultaten, zelfgerapporteerde cognitieve problemen en symptomen van angst en depressie. Subjectieve cognitieve problemen zijn lastig te interpreteren omdat zij sterk multifactorieel bepaald zijn. De zelfgerapporteerde cognitieve problemen in dit proefschrift zouden kunnen worden geïnterpreteerd als een maat voor executieve controle, waarbij individuen met symptomen van angst en depressie cognitieve problemen ervaren, met name in complexe en stressvolle situaties van alledag. Executief functioneren is een systeem dat verschillende cognitieve functies met elkaar in verband brengt, integreert en de afzonderlijke functies overstijgt. Het geeft sturing en controle over cognitieve processen. Op de executieve functies wordt vooral een beroep gedaan in nieuwe, complexe en onbekende situaties waarin een snelle en efficiënte aanpassing van het gedrag aan de omgeving vereist is en wanneer bekende routinematige oplossingen niet voldoen. In een testsetting zouden problemen kunnen ontstaan op tests die een beroep doen op plannen, werkgeheugen, responsinhibitie en cognitieve flexibiliteit. Echter, een goede prestatie in een gestructureerde testsetting sluit problemen op taken in complexe alledaagse situaties niet uit. In een gestandaardiseerde testsetting is de situatie gestructureerd, worden instructies gegeven en de taken worden een voor een aangeboden. In het dagelijks leven moeten de taken echter zelf gepland en bijgestuurd worden, waarbij vooral problemen optreden in situaties waar multitasking vereist is. De rol van posttraumatische stresssymptomen, hoewel geen onderwerp in dit proefschrift, moet in toekomstig onderzoek worden meegenomen. Het kan, tot slot, niet uitgesloten worden dat de aanwezigheid van cerebrale wittestofaflaesies en subjectieve cognitieve problemen in vrouwen na eclampsie of pre-eclampsie een voorbode zijn voor de ontwikkeling van cognitieve dysfunctie op latere leeftijd. De bevindingen in dit proefschrift onderstrepen het recente gedachtegoed dat pre-eclampsie een aandoening is met gevolgen voor het geheel van emotionele, cardiovasculaire en cerebrovasculaire gezondheid op de lange termijn. Alhoewel dit proefschrift geen objectief cognitieve dysfunctioneren heeft kunnen

aantonen bij vrouwen na eclampsie of pre-eclampsie, verdienen de gerapporteerde subjectieve cognitieve problemen zorgvuldige aandacht. Hiertoe kunnen follow-up en tijdige interventie om emotioneel welzijn te bevorderen van belang zijn. Daarnaast zou onderzocht kunnen worden of het aanbieden van meer structuur in de planning, uitvoering en monitoring van taken die primair relevant zijn in het alledaags leven mogelijk een effect kan hebben op de subjectieve cognitieve problemen die deze vrouwen ervaren. Toekomstig onderzoek richt zich ook op evaluatie en implementatie van leefstijladviezen gericht op het verminderen van cardiovasculaire en cerebrovasculaire risicofactoren.

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PUBLICATION OVERVIEW

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CURRICULUM VITAE

Curriculum vitae (Nederlands)

Ineke Rixt Postma, geboren op 9 februari 1987, groeide op in Dokkum. Zij bezocht het Gymnasium van het Dockinga Collega en behaalde in 2005 cum laude haar eindexamen met het profiel Natuur & Gezondheid, Latijn en Muziek. In 2005 begon ze met de studie Geneeskunde aan de Rijksuniversiteit Groningen. Na het behalen van haar propedeuse, begon Ineke deel te nemen aan verscheidene activiteiten binnen de Junior Scientific Masterclass (JSM) van het Universitair Medisch Centrum Groningen (UMCG). Haar interesse voor wetenschappelijk onderzoek was gewekt en ze startte met een onderzoeksproject bij de afdeling obstetrie van het UMCG onder begeleiding van dr. G.G. Zeeman. Na het behalen van haar bachelordiploma in 2008 deed zij haar wetenschappelijke stage bij deze afdeling en dit resulteerde uiteindelijk in een promotieonderzoek in het kader van een MD/PhD-traject en dit proefschrift (promotores: prof. dr. J.G. Aarnoudse en prof. dr. A. Bouma). Na haar wetenschappelijke stage bracht Ineke zeven maanden door in Salt Lake City, Utah, U.S.A., om daar onder begeleiding van prof. dr. M.A. Belfort onderzoek te doen naar de cerebrale haemodynamiek tijdens de zwangerschap. Haar coschappen liep zij in het UMCG en het Medisch Centrum Leeuwarden. Haar semi-artsstage deed zij bij de afdeling Obstetrie & Gynaecologie in de Tjongerschans te Heerenveen en haar verdiepingsstage bij het Departement of Maternal, Newborn, Child and Adolescent Health van de World Health Organization (WHO) in Genève, Zwitserland. In het voorjaar van 2014 behaalde zij cum laude haar artsexamen.

Curriculum vitae (English)

Ineke Rixt Postma was born in the Netherlands on February 9, 1987. After obtaining her high school diploma cum laude, she started Medical School at the University of Groningen in 2005. During her studies, she participated in several activities of the Junior Scientific Masterclass (JSM) of the University Medical Center Groningen (UMCG). Her interest in science grew and she started with a research project with Dr. G.G. Zeeman at the department of Obstetrics at the UMCG. After obtaining her bachelor's degree in 2008, Ineke continued doing her research internship there, which resulted in this thesis (promotors Dr.J.G. Aarnoudse and Prof. Dr. A. Bouma). She spent seven months in Salt Lake City, Utah, USA, working on cerebral haemodynamics in pregnancy with Prof. Dr. M.A. Belfort. Ineke furthered her medical training at the UMCG and the Medical Center of Leeuwarden. Her elective rotation was done at the department of Obstetrics & Gynaecology at the Tjongerschans hospital in Heerenveen and an additional rotation at the Department of Maternal, Newborn, Child and Adolescent Health of the World Health Organization (WHO) in Geneva, Switzerland. She received her cum laude medical degree in the spring of 2014.