Cerebral Manifestations of Preeclampsia

Ingrid Anna Brussé

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Cerebrale manifestaties in preeclampsie

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Contents

CHAPTER 1

Introduction

Introduction

Ten to 15% of all pregnancies are complicated by de novo hypertension (1). Gestational hypertensive disease includes pregnancy induced hypertension and preeclampsia presenting as various phenotypes. In about one third these pregnancies hypertension is accompanied by proteinuria and in 4-12% of these cases additionally complicated by the HELLP (Hypertension Elevated Liver Enzymes Low Platelets) syndrome. Due to generalised endothelial damage there is a multiorgan disease with disturbances in the hematologic system (hemolysis), coagulation cascade (diffused intravascular coagulation), glomerular endotheliosis and liver cell damage.

About one-third of the preeclamptic patients show dysfunction of the central nervous system. Symptoms include headaches, increased tendon reflexes, eclampsia, visual disturbances (flashes, altered colour sensations, visual field loss and cortical blindness) and strokes (both hemorrhagic and ischemic) (2, 3). It can result in maternal death as the ultimate complication. Many former patients after a severe preeclampsia have problems to return to normal life (4).

The internal organs involved in the pathophysiology of preeclampsia can well be monitored with routine biochemical tests. In the current clinical setting the neurological effects can, however, hardly be monitored by objective measures, while 71 % of the maternal deaths due to preeclampsia are caused by cerebrovascular accidents (5).

In a pilot study performed by our research group, Electroencephalography (EEG) was performed in 12 preeclamptic patients and 12 healthy pregnant controls. We studied them in pregnancy and 6 weeks postpartum. In preeclamptic patients significantly more EEG alterations were found as compared to the pregnant controls both in pregnancy as well as postpartum (6).

Others showed EEG abnormalities in up to 80% of the postictal eclamptic patients. It is not known whether these were already present before the onset of the eclampsia (7). Therefore, in this thesis different phenotypes of gestational hypertensive disease were investigated to learn more about the presence of (sub-)clinical cerebral changes.

A rough way to be informed about brain function, especially consciousness, can be by measures like the Glasgow Coma Score. Furthermore, information can be obtained by imaging techniques like Magnetic Resonance Imaging (MRI), functional-MRI (fMRI) or Computer Tomography (CT). An adequate measure for brain function in hypertensive disorders of pregnancy has still to be developed. In this thesis we chose to elaborate on neurophysiologic measures.

The basis of cerebral neurophysiological investigation is Electroencephalography (EEG), which gives an overview of the brain function with modest spatial but very high temporal resolution. The EEG is sensitive to detect cerebral hypoxic changes (8). Since about one-third severe preeclamptic patients show symptoms of visual disturbances,

possibly related to brain function, the study of Visual Evoked Potentials (VEP) can also be informative. Maternal hemodynamics is also disturbed, which can be studied with Transcranial Doppler sonography.

In routine obstetric clinical practice the neurologic agitation level of the preeclamptic patient is monitored with blood pressure measurements together with the assessment of patellar reflexes. An agitated and hypertensive patient is considered at risk for an eclamptic fit.

The interpretation of the patellar reflex is subjective with high inter- and intraobserver variability (9). In the medical literature there are no studies available on the quantification of these reflexes with Electromyography (EMG) in hypertensive pregnancy. Therefor we also assessed the patellar reflex in these patients with EMG in a quantitative way.

General aim of this thesis

This thesis intends to describe and explain the course of clinical neurophysiological and neuropsychological parameters in patients with hypertensive disorders in pregnancy. We aimed to improve knowledge on cerebral pathophysiological mechanisms of preeclampsia related to signs and symptoms and to explore whether measuring features of these mechanisms with neurophysiological techniques can help to optimize timing of delivery in order to minimize maternal morbidity and maximize neonatal outcome.

This thesis contains 9 chapters:

After this introduction this thesis opens with a systematic review of the literature on EEG during normotensive and hypertensive disorders of pregnancy (**chapter 2**). Publications on this subject are of relatively old date and often not consistent with current clinical guidelines or medical terminology. Therefore, further research is needed to investigate the clinical value of implementing EEGs in the assessment of preeclamptic patients.

In **chapter 3** a study is presented on EEG during pregnancy and postpartum, both in normotensive and hypertensive women. Subsequent quality of life was tested postpartum, using Health related quality of life (HRQoL) questionnaires with physical, psychological and social domains. In **chapter 4** the results are shown of a study on visual evoked potentials (VEPs) in normotensive, chronically hypertensive and preeclamptic women.

As cerebral perfusion pressure (CPP) is elevated in preeclampsia (10), CCP was studied in preeclamptic women and healthy pregnant controls in **chapter 5**. We estimated zero flow pressure (ZFP) and CPP using simultaneously obtained arterial blood pressure (ABP) and middle cerebral artery blood flow velocity.

The study in **chapter 6** compared electromyographically recorded patellar reflex in normotensive and preeclamptic pregnancies.

In **chapter 7** the neuropsychological outcome is presented of women three to eight months after severe preeclampsia. We compared a group of formerly preeclamptic women with a group of women with previous normotensive pregnancies, using a battery of neuropsychological tests.

Chapter 8 and **9** provides a general discussion and a summary of this thesis.

Literature

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631-44.
2. Jaffe G, Schatz H. Ocular manifestations of preeclampsia. Am J Ophthalmol. 1987;103:309-15.
3. Marsh MS, Smith S. Differences in the pattern visual evoked potential between pregnant and non-pregnant women. Electroencephalogr Clin Neurophysiol. 1994;92:102-6.
4. Gaugler-Senden IP, Duivenvoorden HJ, Filius A, De Groot CJ, Steegers EA, Passchier J. Maternal psychosocial outcome after early onset preeclampsia and preterm birth. J Matern Fetal Neonatal Med. 2012;25:272-6.
5. Schutte JM, Schuitemaker NW, van Roosmalen J, Steegers EA, Dutch Maternal Mortality C. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. BJOG. 2008;115:732-6.
6. Brusse IA. Neurophysiologic surveillance of the brain in (pre)eclampsia, is it worthwile? ISSHP; 07/2006; Lisbon2006.
7. Thomas SV. Neurological aspects of eclampsia. J Neurol Sci. 1998;155:37-43.
8. Amantini A, Carrai R, Lori S, Peris A, Amadori A, Pinto F, et al. Neurophysiological monitoring in adult and pediatric intensive care. Minerva Anestesiol. 2012;78:1067-75.
9. Stam J, van Crevel H. Reliability of the clinical and electromyographic examination of tendon reflexes. Journal of neurology. 1990;237:427-31.
10. Belfort MA, Varner MW, Dizon-Townson DS, Grunewald C, Nisell H. Cerebral perfusion pressure, and not cerebral blood flow, may be the critical determinant of intracranial injury in preeclampsia: a new hypothesis. Am J Obstet Gynecol. 2002;187:626-34.

CHAPTER 2

Electroencephalography during normotensive and hypertensive pregnancy: A systematic review

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Abstract

The objective of this review was to evaluate the available medical literature concerning the electroencephalogram (EEG) during hypertensive disorders of pregnancy. All articles found during a MEDLINE and Embase database search on the subject of EEG differences associated with hypertensive disorders in pregnancy were screened for elegibility. Twenty-two articles which describe the EEG during preeclampsia (PE)/ eclampsia were retrieved. Abnormal EEG findings were observed in the majority of the preeclamptic/ eclamptic patients, consisting of slow waves most frequently localized in the occipital lobe, as well as spike discharges. The EEG abnormalities in PE/eclampsia were reversible in the majority of cases. We conclude that these described abnormalities may be interpreted as a warning sign of deterioration of brain function in PE/eclampsia. However, some caution regarding this conclusion is advised because most of the retrieved articles were published in the 1950s and 1960s, and were not consistent with current clinical guidelines or medical terminology. Further research is needed to establish the clinical value of implementing EEGs in the assessment of the preeclamptic/eclamptic patient.

Introduction

Hypertensive disorders of pregnancy (pregnancy induced hypertension (PIH), pre-eclampsia (PE) and eclampsia) affect at least 5-8% of all pregnancies and are a leading cause of global maternal and infant morbidity and mortality (1). In developed countries, related maternal mortality is primarily caused by cerebrovascular complications (2).

According to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP), PIH is defined as de novo hypertension after 20 weeks of gestation, PE as the combination of hypertension and proteinuria (3). The severity of PE can be defined according to the criteria of the American College of Obstetricians and Gynecologists (ACOG) (4). A serious complication is an eclamptic seizure, resembling an epileptic grand mal seizure.

Deterioration of the preeclamptic symptoms and prevention of maternal complications can solely be achieved by delivery of the fetus and placenta. At present, the timing to terminate the pregnancy is predominantly based on clinical assessment, taking in consideration gestational age.

In pregnancies complicated by hypertensive disorders, neurological symptoms like headache and visual disturbances are important symptoms possibly reflecting brain function disorders. Electroencephalography (EEG) is known to be a sensitive method to detect brain dysfunction. EEG changes can be found before clinical symptoms are present and before ischemic conditions may result in irreversible brain dysfunction (5). So far, EEG changes do not play a role in the assessment and management of (pre-)eclamptic patients.

The aim of this review was to study the literature on EEG findings in hypertensive disorders of pregnancy. To our knowledge, no reviews on this subject have been published so far. To improve the interpretation of the reported results, we also reviewed the literature on EEG differences in (young) men and women, during the menstrual cycle and in normotensive pregnant and non-pregnant women.

Background

Electroencephalography

Electroencephalography is a method to record the electrical activity generated by the brain. The electrical activity of the brain reflects the normal function of active neuronal networks. Abnormal brain function is often reflected in changes in this electrical activity, especially for more acute and extensive lesions. As such, EEG changes are in general not very specific, but have a fair to good sensitivity for the detection of, for instance, cerebral hypoxia. In addition, EEG is the only method to detect electrical epileptiform

activity. Findings like spike-wave complexes have a high sensitivity and specificity in the diagnosis of an epileptic disorder.

Routinely EEGs are recorded by the 10-20 International System of Electrode Placement. In this system the names and location of the electrodes are specified and related to the brain areas (frontal, central, temporal, parietal and occipital). In most clinical applications, 19 recording electrodes (plus ground and system reference) are used. Registrations are made for a period of 20 to 30 minutes, including standardized provocations like light flash stimulation and hyperventilation, and usually a period of light sleep for 15 minutes is allowed.

The various EEG activities can be divided into background activity, focal abnormalities, and intermittent and paroxysmal activity. The background activity consists of alpha-, beta-, delta- and theta-activity (see textbox). In reviewing the EEG, abnormalities in waveform, frequency, amplitude, symmetry, and reactivity patterns (i.e. slow waves or spikes/spike-wave complexes) are documented, including the localization (focal versus diffuse/generalized). In clinical practice, assessment of the EEG is largely based on a visual review of the recording and is hindered by large inter-individual variation.

Frequency spectral analysis like Fast Fourier analysis is a quantitative EEG (qEEG) method used to objectively quantify the contributions of the various frequencies, for instance in the conventional frequency bands (see textbox). The amount of activity in a certain frequency band can be expressed as power (squared amplitude), as an absolute value, or in relation to the total power of all frequencies in the spectrum. Another variable from a power spectrum may include the frequency corresponding to a prominent peak in the spectrum (like the alpha peak frequency). The alpha peak frequency is one of the more reliable variables for which reference values are available.

Textbox
Frequency bands of the EEG (9)

Waves	Frequency	Description
Delta	2.0~3.75 Hz	They are present in babies, certain forms of encephalopathy and during sleep
Theta	4.0~7.75 Hz	They are present in children, during snoozing, (day) dreaming, light sleep and just before waking up or falling asleep. They can be generated by trance or hypnosis
Alpha1	8~9.75 Hz	Important activity in the alpha-range is the so called alpha-rhythm. This rhythm is characterized by an occipital localization and suppression by opening of the eyes
Alpha2	10.00~12.75 Hz	
Beta1	13.00~19.75 Hz	If they have low amplitude and multiple frequencies they are related to intensive thought and concentration. Rhythmical beta-waves with many pronounced frequencies reflect pathological or drug-related causes
Beta2	20.00~30.00 Hz	

EEG differences between men and women

Nine articles describe EEG differences between men and women (6-15). For individuals aged 20 to70 years, the power of the theta and beta-frequencies are higher in females in most derivations, whereas the power of the alpha-frequency is higher in males in the parieto-occipital derivations (13, 15). Females have a greater asymmetry in cerebral activity during tasks (divergent thinking, mental rotation tests, and verbal fluency tests) than males. When hemispheric integration is mandatory, men and women show similar asymmetry in EEG patterns (6-8, 10-11).

One study's quantitative frequency analysis shows that women have significantly smaller absolute amplitudes (in μV) than men in the theta (20.6±9.5 versus 23.6±10.8), alpha1 (8-10Hz; 18.1±11.4 versus 22.9±15.8), alpha2 (10-13 Hz; 28.8±19.5 versus 34.9±19.7) and beta2 (20-25 Hz; 16.3±7.8 versus 18.5±7.6) bands, measured in the derivations from occipital to midline (see textbox). The absolute amplitudes of all frequency bands are also significantly smaller in women in the derivations from occipital to central: delta (12.0±7.8 versus 16.7±8.8), theta (21.5±12.3 versus 28.2±15.6), alpha1 (18.9±13.8 versus 29.0±24.3), alpha2 (28.3±22.7 versus 38.3±22.7), beta1 (21.3±12.4 versus 26.4±15.1) and beta2 (16.0±9.3 versus 20.1±10.6) (9). However, Ellis described higher amplitudes of beta-frequencies in the right occipital lobe in women (14). The clinical or physiological significance of these changes is not known. These gender differences may partly reflect functional anatomical differences between men and women. They may also be attributed to differences in hormonal patterns, a hypothesis that is supported by studies performed during the menstrual cycle.

EEG during the menstrual cycle

In eight studies investigating this subject there appears to be a correlation between the physiological hormonal fluctuations during the menstrual cycle and EEG findings: during the follicular phase, as estrogen levels are rising, there is a slower alpha-rhythm (alpha1-range) and an increase of power in the theta-frequency range (16-19). During the ovulatory phase, there is a lower power of alpha-rhythm in the EEG spectrum and higher interhemispheric correlations between frontal derivations (20-21). During the luteal phase, higher interhemispheric correlations between occipital derivations are seen (21). There is also a faster alpha-rhythm during the luteal phase; the mean frequency varies within the alpha2-range (10.3–14.1 Hz) measured by using Fast Fourier Transform analysis (16-18, 22). It has been suggested that the changes observed during the luteal phase are related to rising progesterone levels. Contreras et al. are the only investigators who have reported a decrease in alpha-frequency in the luteal phase compared to the follicular phase (23). Smaller cycle stage-dependent differences in the power of the theta- and

beta-bands have also been reported (16). During the premenstrual period, the power of delta, theta, and alpha1 (frequency of 7.5-9.5 Hz) has been reported to be higher. Theta-activity has also been reported to be twice as common in EEGs obtained during the premenstrual period as in records obtained during other parts of the menstrual cycle (17). These results were not further quantified. During menstruation the power of the alpha2 (9.5-12.5 Hz), beta1 (12.5-17.5 Hz) and beta2 (17.5-30 Hz) have been reported to be higher (20-21).

Most studies of EEG changes during the menstrual cycle have not attempted to determine the clinical or physiological meaning of the reported differences. A lower alpha-frequency and increased theta-frequencies might reflect a slight decrease in brain function. However, in clinical practice, changes in alpha-frequency within one patient are usually regarded as clinically significant only if larger than 1 Hz, and the reported changes are not of this level.

EEG during normal pregnancy

Keunen investigated differences between EEG findings during the 3rd trimester of pregnancy and six months postpartum, and found no differences in spectral EEG analysis(24). No information on hormonal or lactation status was given. Poidevin (25) found EEG anomalies in 15% of the normotensive pregnant women, which is not significantly different from the incidence of EEG anomalies in the general population (14%) (26).

Chiang (27), Poidevin (25), and Sibai (28) used normotensive pregnant women as control group in their studies on hypertensive pregnancies. Chiang (27) described all EEGs as being within normal limits, based on visual assessment and Fourier analysis; no EEG anomalies were seen. However, alpha-rhythm frequencies were <8 Hz in 14%, and today <8 Hz is usually regarded as an abnormal frequency. Sibai (28) found in 15% of normotensive pregnant women diffuse slowing in the theta-range frequencies.

The clinical relevance of these EEG changes during normal pregnancy has never been studied. However, a tentative hypothesis is that the EEG changes are associated with some frequently experienced cognitive problems during pregnancy, such as forgetfulness and diminished mental alertness (29).

Search strategy

Searches were performed using MEDLINE and Embase databases with the following limits: language (English, German, French and Dutch) and human. All case-control studies executed between 1950 and January 2009 were considered eligible if they described

EEG results in adults in relation to hypertensive disorders in pregnancy. References of the retrieved articles were also screened for eligibility.

Search terms for EEG differences between normotensive and hypertensive pregnant women were searched using the search terms ("electroencephalography" or "EEG") and ("pregnancy induced hypertension" or "preeclampsia").

Excluded were articles discussing sleep EEGs and articles, which were not retrievable. Reviews, case reports and case series were only used for screening of the references. This review is written according to the QUORUM statement (30).

Search results

The search on hypertensive disease in pregnancy yielded 65 accessible articles (see figure). These potentially relevant articles were first screened by abstract. Based on reviewing the abstracts we excluded 15 articles, since the subject of the article was not to describe quantitative EEG alterations. After screening the remaining 50 articles for more detailed evaluation, 21 more articles were excluded. These articles were excluded because it became apparent that the article did not describe possible changes in EEG patterns during hypertensive disorders in pregnancy. Since we only wanted to include articles describing case-control studies in our review, 21 more articles were exclude, including six reviews (31-36), nine case reports (37-45) and six case series.(26, 46-50) These papers were used only for screening the references.

The final search resulted in eight eligible case-control studies (25, 27-28, 51-55), which are summarized in table 1. These studies describe 782 pregnant women with hypertensive disease. Cases were compared with normotensive (pregnant) women, men or epileptic patients.

EEG findings in pregnancy with essential hypertension

Slow waves (<8 Hz) were found in 15.3% of the EEGs obtained from women with essential hypertension, whereas 2.8% of the EEGs showed fast waves (>13 Hz). All of the EEGs (cases and controls) showed moderate amplitude; high voltages were only found in the hypertensive cases (27).

EEG findings in preeclampsia

Preeclamptic patients were included in seven of eight available studies (a total of 179 patients, table 2). The incidence of EEG abnormalities in these women ranged from 5% (n=3) to 50% (n=7), with an average of 29% (25, 27-28, 51-52, 54-55).

Table 1 Characteristics of included studies

Case-control studies	Level of evidence	Participants	Results
Osmanagaoglu et.al. 2005	Level 2B	15 mild PE	EEG abnormalities in 20% (n=3) *Diffuse slowing:* 13,3% (n=2) *Focal slowing:* 6,7% (n=1) in the left posterior area
		11 severe PE	EEG abnormalities in 27,3% (n=3) *Diffuse slowing:* 18,2% (n=2) *Focal spike discharges:* 9,1% (n=1) in the right hemisphere posterior area
		12 E	EEG abnormalities in 58,3% (n=7) *Diffuse slowing:* 25% (n=3) in one located in the right hemisphere *Focal slowing:* 8,3% (n=1) in the left occipital lobe *Focal spike discharges:* 16,7% (n= 2) in one multifocal and in one in the left posterior area *Diffuse spike discharges:* 33,3% (n=4)
Sibai et. Al. 1984	Level 2B	14 PE	*Diffuse slowing:* 50% (n=7) in the form of theta-/delta-waves
		36 E	EEG abnormalities in 75% (n=27) *Diffuse slowing:* 40% (n=14) *Focal slowing:* 33% (n=12) *Paroxysmal spike discharges:* 11% (n=4) of which 2 had clinical seizure activity
		13 NTP	*Diffuse slowing:* 15,4% (n=2) women showed diffuse slowing In general: significantly more abnormal EEGs in PE and E compared to NTP
Chiang et. al. 1964	Level 3B	18 mild PE	EEG abnormalities in 33,4% (n=6) *Fast waves:* 29,75% of the EEGs showed fast waves (>13 Hz)
		7 PE	EEG abnormalities in 42,9% (n=3)
		2 E	EEG abnormalities in 100% (n=2) *Slow waves:* 17,2% of the EEGs (<8 Hz) *Fast waves:* 1,0% of the EEGs (>13 Hz)
		16 NTP	*Slow waves:* 13,5% of the EEGs (<8 Hz) *Fast waves:* 6,2% of the EEGs (>13 Hz)

Table 1 Characteristics of included studies (continued)

Case-control studies	Level of evidence	Participants	Results
		14 EH	EEG abnormalities in 28,5% (n=4) *Slow waves:* 15,3% of the EEGs (<8 Hz) *Fast waves:* 2,8% of the EEGs showed fast waves (>13 Hz)
Ezes et. al. 1960	Level 3B	4 PE	Pathological synchronisations and voltages in fast rhythms →they are favourable for diffuse electrogenises with a metabolic origine
		21 E	EEG abnormalities in 85,7% (n=18) *Diffuse or focal polymorphic delta-waves:* 38,1% (n=8) *Pre-existent dysrhythmias:* 9,5% (n=2) *Fast waves:* 52,4% (n=11) which disappeared completely in 3, and 8 developed epileptic activity in the temporal leads
		2 epileptic patients	No traces of diffuse cerebral alterations *Acceleration peaks* in the temporal area
Geiser-Rauch et. al. 1958	Level 3B	14 E	*At rest* 3 EEGs showed remarkable flat potentials & 1 EEG showed very high potentials *During hyperventilation* 3 EEGs showed non-specific mild changes which consist of small 4-6 Hz waves & 1 EEG showed bitemporal a few spikes *During the triplex test* 2 EEGs showed an diffuse dysrythmic reaction (dosage: 4,4-5,5 mg/kg), 10 EEGs showed bilateral low voltage (mean dosage: 3,3 mg/kg), 9 EEGs showed high slow paroxysmal waves (mean dosage: 4,5 mg/kg), 1 EEGs showed bitemporal a few spikes (dosage: 2,9 mg/kg) & 1 EEG showed arrhythmic spike waves without a clinical myocyclonic attack
		50 male and female students	*At rest* there were often deviations seen from the classic alpha-rhythm (no indication of an abnormal reaction) *During hyperventilation* few people showed an elevated amplitude *During light stimulation* 5 people showed no reaction (mean dosage: 7,9 mg/kg), 34 people showed bilateral low voltage (mean dosage 2,4 mg/kg), 26 people showed bilateral high slow paroxysmal synchronized waves (mean dosage 4,5 mg/kg), 6 people showed multifocal spike waves (mean dosage 4,7 mg/kg) & 2 people showed focal spikes (dosage: 1,4-5,1 mg/kg)
Colle et. al. 1956	Level 3B	14 postpartum PE	EEG abnormalities in 28,6% (n=4) in the occipital area recordings. *Subnormal EEGs in 42,9% (n=6)*

Table 1 Characteristics of included studies (continued)

Case-control studies	Level of evidence	Participants	Results
		23 E	EEG abnormalities in 26,1% (n=6) bilateral occipital slowing (3-4 Hz) and paroxysmal dysrhythmia. No paroxysmal abnormalities or lateralisation *Subnormal EEGs in 56,5% (n=13)* General conclusion: no differences were seen in EEG patterns between pre-eclamptic and eclamptic patients
Poidevin 1955	Level 3B	12 mild PE 8 moderate PE 13 severe PE	EEG abnormalities in 24% (n=8) in patients with all grades of PE
		12 E	EEG abnormalities in 83% (n=10)
		34 NTP	EEG abnormalities in 15% (n=5)
Janzen et. al. 1952	Level 3B	63 PE	*Slow waves:* 4,8% (n=3)
		16 E	EEG abnormalities in all women, which are identical to those seen in epilepsy
		18 former E	No EEG abnormalities

PE = preeclampsia, E = eclampsia, NTP = normotensive pregnant women, EH = essential hypertension

Table 2 Validity testing included case-control studies

	Defining	Trial design	Patient selection criteria	Correction for selectionbias	Blinded outcome	Follow-up	Valid
Osmanagaoglu et al. 2005	+	+	+	+	NP	+	√
Sibai et al. 1984	+	+	+	-	+	+	√
Chiang et al. 1964	-	-	+	-	NP	NP	x
Ezes et al. 1960	-	-	-	-	NP	NP	x
Geiser-Rauch et al. 1958	-	+	+	-	NP	NP	x
Colle et al. 1956	-	+	+	-	NP	-	x
Poidevin 1955	-	+	-	-	+	NP	x
Janzen et al. 1952	-	-	-	-	NP	NP	x

\+ sufficient
\- insufficient
NP not performed

√ valid research according to current standards
x non-valid research according to current standards

The different types of anomalies found in preeclamptic patients were described as: diffuse slowing (n=4/26) (55), diffuse slowing in the form of theta/delta-waves (n=7/14) (28), focal slowing in the left posterior area (n=1/26) (55), focal spike discharges in the right hemisphere posterior area (n=1/26) (55), and pathological synchronizations and voltages in fast rhythms (52). The distinction between mild and severe preeclampsia was defined in only one report (Pritchard definition) (55); in another paper no definition was given (25). No significant differences were found between women defined as having mild versus severe preeclampsia (25, 55). Janzen (54) found normal EEGs in 95.2% (n=60/63) of preeclamptic patients. One of the women showed minor abnormalities, which were nearly within the normal range, and two other patients showed slowing. A higher incidence of "cerebral irritation" in all patients with a hypertensive pregnancy was described by Poidevin (25).

The EEGs recorded postpartum in preeclamptic patients by Colle were considered to be "normal" in 29% (n=4/14), "subnormal" (not further defined) in 43% (n=6/14) and "pathological" in 29% (n=4/14) of the patients. These pathological EEGs showed anomalies in the occipital area recordings (51).

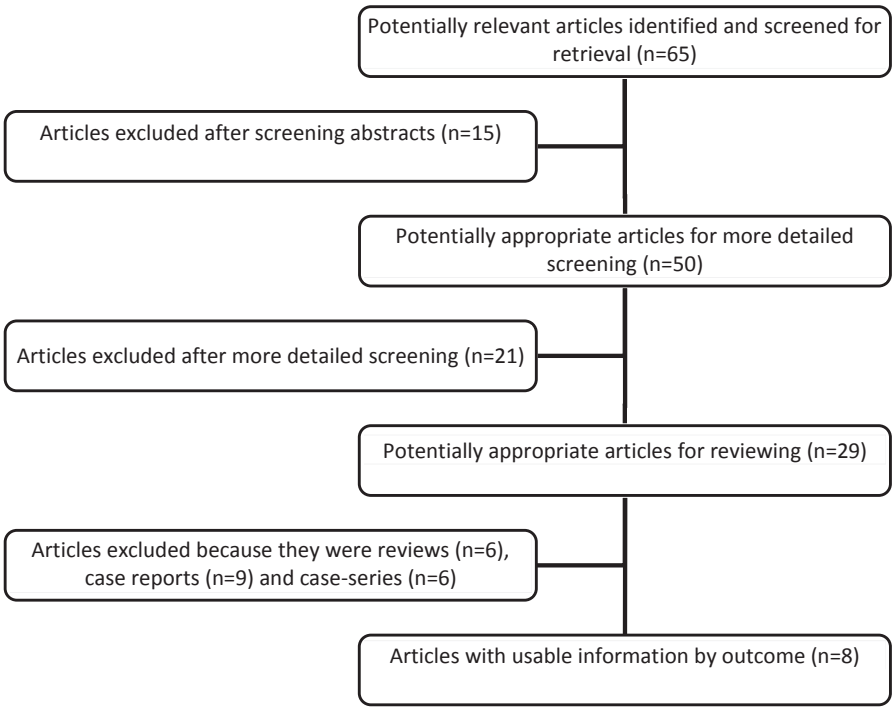

Figure
Articles suitable for reviewing

EEG findings in eclampsia

A total of 153 eclamptic patients were included in the eight available studies (25, 27-28, 51-55). The incidence of abnormalities in these studies varied from 59% to 100%. On average, 81% of the EEGs of eclamptic women showed abnormalities.

Janzen et al. (54) stated that an EEG can be used to determine whether an intrapartum seizure represents eclampsia or an epileptic seizure during labor. This group also reported that some EEG abnormalities, which are seen in eclamptic women one to three weeks postpartum, resemble those seen in an epileptic patient after a seizure. The EEG recordings obtained several years after eclampsia do not contain any abnormalities. Ezes et al. found no traces of diffuse cerebral alterations in eclamptic patients, but they did find acceleration peaks in the temporal area (52).

Of the 153 eclamptic patients included in these studies, 48% (n=30) with EEG abnormalities showed slowing (25, 28, 51, 55). Diffuse slowing was described in seventeen women (28, 55); in one patient this was restricted to the right hemisphere (55). Focal slowing was found in thirteen of them (28, 55); in one it was located in the left occipital lobe (55).

Spike discharges were found in ten eclamptic patients (28, 55). Five patients showed multifocal or diffuse spike discharges (55); one patient presented focal spike discharges in the left posterior area (55) and four patients showed paroxysmal spike activity (of which two had clinical seizures) (28). Thirteen of the eclamptic patients examined by Colle (51) showed "subnormal" (not further defined) EEGs; six of these patients had pathological EEGs containing bilateral abnormalities, occipital slowing (3-4 Hz) and paroxysmal anomalies.

Ezes (52) found diffuse or polymorphic delta-waves in eight patients and epileptic activity in the temporal area in four patients; these EEG anomalies were interpreted as prodromal for an eclamptic seizure. Chiang (27) examined the percentage EEG activity in the various frequency bands; 17.2% of the waves seen on the EEGs of eclamptic patients were slow waves (<8 Hz) and 1.0% of the observed waves were considered fast waves (>13 Hz).

Geiser-Rauch et al (53) performed provocation tests by means of hyperventilation and triple activation (a combination of Cardiazol, Narconumal and stroboscope) to eclamptic patients. In twelve of fourteen eclamptic patients, the EEGs were abnormal during the triple activation test; two showed a diffuse dysrhythmic reaction, ten showed bilateral low voltage, nine showed high slow paroxysmal waves, one showed a few bitemporal spikes and another showed arrhythmic spike waves without a clinical myoclonic attack. There were no significant EEG differences between eclamptic women and controls (both male and female students) at rest (53). However, during triple-activation a significant difference was seen: in the majority of eclamptic patients, there was latent brain stem sensitivity (bilateral synchronized waves).

EEG in preeclamptic versus eclamptic women

Osmanagaoglu found significantly (P<0,05) more abnormal EEGs in eclamptic patients than in either mild or severe preeclamptic patients (defined according to the ACOG criteria) (55). However, Colle (51) found no differences in EEG patterns between preeclamptic and eclamptic patients.

Clinical symptoms and EEG abnormalities

In three studies, clinical findings, including mean arterial blood pressure in two studies, were documented in addition to EEG findings (27-28, 55). No correlations were found between mean arterial blood pressure and EEG abnormalities. However, Chiang (27) reported that clinical manifestations occurred more often in the patients with abnormal EEGs than in those with normal EEGs (40% (n=6/15) versus 24% (n=6/26).

In the study performed by Osmanagaoglu (55) a significant (P<0,05) correlation was found between EEG findings and MRI (magnetic resonance imaging) studies; abnormal EEG findings were found in 87.5% (n=14) patients, both preeclamptic and eclamptic, who had MRI abnormalities. Three patients had only EEG abnormalities, and two patients had only MRI abnormalities.

Discussion

Since the majority of the studies we reviewed were published more than 20 years ago, we assessed the validity of the different studies according to current standards. The results of our validity assessment can be found in table 2. The most important items of the assessment will be described in the following paragraphs.

Six of the eight case-control studies were published before 1967 (25, 27, 51-54). The remaining two articles were published in 1984 (28) and 2005 (55). The first international definition of preeclampsia was adopted by the World Health Organization in 1985, and defined in the ACOG Technical Bulletin in 1986 (56). In their studies, Sibai et al. (28) used criteria defined in the obstetric handbook written by Pritchard (57), and Osmanagaoglu et al. (55) used ACOG criteria. Furthermore, several authors subdivided their groups of patients with hypertensive disorders of pregnancy into categories that do not correspond with current definitions. For example, Chiang et al. (27) refers to "mild" eclamptic patients, and Poidevin (25) speaks of "moderate" preeclampsia and "moderate" eclampsia.

The method by which an EEG is described and interpreted has changed over the years, and over time has been standardized. It is difficult to translate the descriptions of the EEGs in these older papers into current medical terminology. For example Colle et al. (51) and Janzen et al. (54) did not specify which definitions they used to divide the EEG recordings into "normal", "subnormal" or "pathological". Similarly, Iwanow (46) used terms such as "instable" and "slow acting", but did not clarify what was meant. The term 'dysrhythmia' was used frequently (25-26, 51), but its use is currently discouraged in the official glossary of terms (58) since it does not specify the type of disturbance.

Several of the papers we reviewed had design flaws. For example, in three of the eight case-control studies we reviewed (27, 46, 53), more than one EEG per patient was included. These EEGs were evaluated as individual EEGs instead of as being representative of one patient, a policy that would artificially inflate the number of abnormal EEGs reported since, once EEG abnormalities occur in a patient, it is likely that subsequent EEGs in that patient will also be abnormal.

The reviewed articles indicated that there are minor differences in EEGs between men and non-pregnant women (6-15). Women show a more dynamic cerebral system, greater cerebral asymmetry during tasks, and more interhemispheric coherence. These gender

differences may be related to hormonal and anatomical differences. This explanation is supported by studies performed to evaluate the EEGs differences during the menstrual cycle. In menstruating women, there appears to be a correlation between estrogen and progesterone levels and alpha-waves in EEG recordings; slower alpha-waves occur during the follicular phase and faster alpha waves are apparent during the luteal phase. Unfortunately, there have been no proper studies that evaluated EEG differences between normotensive healthy pregnant women and non-pregnant women. In the report by Keunen et al. (24) the authors do not mention whether the puerperal women breastfed or not. Since hormonal status only becomes normal after breastfeeding has been discontinued, this may have influenced their results.

The observed EEG changes during the menstrual cycle and the EEG differences between the sexes seem not to be relevant to clinical practice. In the normal population, (mild) EEG anomalies can be found without associated clinically recognizable symptoms, and new EEG waveforms are still being identified (59). However, the EEG does appear to be slightly different in men compared to women and also appears to correlate with hormone levels. In future studies, the influence of confounding factors could be limited by using normotensive pregnant women as controls in clinical studies of EEG changes in hypertensive pregnancies.

In the studies we reviewed, diffuse or focal slow activity, most frequently localized in the occipital lobe, was the most common abnormal activity seen in EEGs made in both eclamptic and preeclamptic women, and there are no clear differences in these EEG findings between mild and severe preeclamptic women. Spike discharges were described in the majority of eclamptic women. The review articles we evaluated (31-36) indicated that neither the severity of the preeclampsia nor the observed EEG alterations are predictive of the occurrence of eclampsia. The case-reports and case-series we reviewed (26, 37-50) provided no additional information.

Hypertensive encephalopathy is caused by the multifocal extravasation of fluid and proteins across the blood–brain barrier during 'breakthrough' of cerebral auto-regulation. MRI has been useful in demonstrating the parieto-occipital high signal intensities involving the cortex and subcortical white matter, which are typical of preeclampsia, and can also determine whether there was permanent damage caused by ischemia. The reported MRI abnormalities included white and grey matter lesions indicating ischemia. The authors suggest that the combined use of EEG and MRI may help to determine the prognosis for these patients (55).

After reviewing the studies we selected, we conclude that the current value of these articles is limited. As mentioned in our introduction, electroencephalography is known to be a sensitive method to detect brain dysfunction due to hypoxia before clinical symptoms are present, and before ischemic conditions result in irreversible brain dysfunction. Therefore, it would be useful to perform more research on electroencephalography in

hypertensive gestational disease, according to current guidelines for EEG interpretation and using current medical terminology. This research should provide more detailed information concerning the type and localization of EEG anomalies associated with PE/eclampsia.

In summary, our review shows that the EEG abnormalities that occur in association with in preeclampsia are reversible in the majority of cases. It is not yet clear whether these EEG abnormalities should be interpreted as a warning sign of deterioration of brain function due to PE/eclampsia. We hypothesize that EEGs may be used in the future to assess the severity of (pre-)eclampsia-associated encephalopathy, in order to determine when medical delivery or other medical interventions are needed.

Literature

1. Steegers EA, von Dadelszen P, Duvekot JJ, et al. Pre-eclampsia. Lancet. 2010 Aug 21;376:631-44.
2. Schutte JM, Schuitemaker NW, van Roosmalen J, et al. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. Bjog. 2008 May;115:732-6.
3. Brown MA, Lindheimer MD, de Swiet M, et al. The classificantion and diagnosis of the hypertensive dysorders of pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertension in Pregnancy. 2001;20:9-14.
4. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002 Jan;99:159-67.
5. Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. J Clin Neurophysiol. 2004 Sep-Oct;21:341-52.
6. Razumnikova OM. Gender differences in hemispheric organization during divergent thinking: an EEG investigation in human subjects. Neurosci Lett. 2004 May 27;362:193-5.
7. Rescher B, Rappelsberger P. Gender dependent EEG-changes during a mental rotation task. Int J Psychophysiol. 1999 Sep;33:209-22.
8. Hausmann M, Gunturkun O. Sex differences in functional cerebral asymmetries in a repeated measures design. Brain Cogn. 1999 Dec;41:263-75.
9. Kaneda Y, Nakayama H, Kagawa K, et al. Sex differences in visual evoked potential and electroencephalogram of healthy adults. Tokushima J Exp Med. 1996 Dec;43:143-57.
10. Beaumont JG, Mayes AR, Rugg MD. Asymmetry in EEG alpha coherence and power: effects of task and sex. Electroencephalogr Clin Neurophysiol. 1978 Sep;45:393-401.
11. Davidson RJ, Schwartz GE, Pugash E, et al. Sex differences in patterns of EEG asymmetry. Biol Psychol. 1976 Jun;4:119-38.
12. Buchsbaum MS, Henkin RI, Christiansen RL. Age and sex differences in averaged evoked responses in a normal population, with observations on patients with gonadal dysgenesis. Electroencephalogr Clin Neurophysiol. 1974 Aug;37:137-44.
13. Smith SM. Discrimination between electro-encephalograph recordings of normal females and normal males. Ann Eugen. 1954 Mar;18:344-50.
14. Ellis NW, Last SL. Analysis of the normal electro-encephalogram. Lancet. 1953 Jan 17;1:112-4.
15. Veldhuizen RJ, Jonkman EJ, Poortvliet DC. Sex differences in age regression parameters of healthy adults--normative data and practical implications. Electroencephalogr Clin Neurophysiol. 1993 Jun;86:377-84.
16. Becker D, Creutzfeldt OD, Schwibbe M, et al. Changes in physiological, EEG and psychological parameters in women during the spontaneous menstrual cycle and following oral contraceptives. Psychoneuroendocrinology. 1982;7:75-90.
17. Leary PM, Batho K. Changes in the electro-encephalogram related to the menstrual cycle. S Afr Med J. 1979 Apr 21;55:666.
18. Creutzfeldt OD, Arnold PM, Becker D, et al. EEG changes during spontaneous and controlled menstrual cycles and their correlation with psychological performance. Electroencephalogr Clin Neurophysiol. 1976 Feb;40:113-31.

19. Gautray JP, Garrel S, Eberard A. [Variations of the electroencephalogram during the menstrual cycle]. Rev Fr Gynecol Obstet. 1970 May;65:257-62.

20. Vasil'eva VV. Spectral and coherent characteristics of EEG in women during various phases of menstrual cycle. Bull Exp Biol Med. 2005 Oct;140:383-4.

21. Solis-Ortiz S, Ramos J, Arce C, et al. EEG oscillations during menstrual cycle. Int J Neurosci. 1994 Jun;76:279-92.

22. Wuttke W, Arnold PM, Becker D, et al. Changes in the EEG during menstrual cycle of women with and without oral contraceptives. Prog Brain Res. 1975;42:322.

23. Contreras CM, Marvan ML, Alcala-Herrera V, et al. Relations between anxiety, psychophysiological variables and menstrual cycle in healthy women. Bol Estud Med Biol. 1989 Jan-Jun;37:50-6.

24. Keunen RW, Vliegen JH, van der Pol DA, et al. The electroencephalogram during normal third trimester pregnancy and six months postpartum. Br J Obstet Gynaecol. 1997 Feb;104:256-8.

25. Poidevin LO. An electroencephalographic study of patients with toxaemia of pregnancy and controls. J Obstet Gynaecol Br Emp. 1955 Jun;62:417-20.

26. Aresin L. [Neurological, psychic and electroencephalographic disorders in late pregnancy toxemias.]. Z Arztl Fortbild (Jena). 1962 Feb 1;56:146-51.

27. Chiang M, Tan YT, Feng YK. Electroencephalographic Study of Toxemia of Pregnancy. Chin Med J (Engl). 1964 Apr;83:227-40.

28. Sibai BM, Spinnato JA, Watson DL, et al. Effect of magnesium sulfate on electroencephalographic findings in preeclampsia-eclampsia. Obstet Gynecol. 1984 Aug;64:261-6.

29. Brusse I, Duvekot J, Jongerling J, et al. Impaired maternal cognitive functioning after pregnancies complicated by severe pre-eclampsia: a pilot case-control study. Acta Obstet Gynecol Scand. 2008;87:408-12.

30. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999 Nov 27;354:1896-900.

31. Thomas SV. Neurological aspects of eclampsia. J Neurol Sci. 1998 Feb 18;155:37-43.

32. Barton JR, Sibai BM. Cerebral pathology in eclampsia. Clin Perinatol. 1991 Dec;18:891-910.

33. Royburt M, Seidman DS, Serr DM, et al. Neurologic involvement in hypertensive disease of pregnancy. Obstet Gynecol Surv. 1991 Oct;46:656-64.

34. Kolstad P. The practical value of electro-encephalography in pre-eclampsia and eclampsia. Acta Obstet Gynecol Scand. 1961;40:127-38.

35. Hootsmans WJ, Van Prooije JA. [The eclampsia problem.]. Schweiz Arch Neurol Psychiatr. 1957;80:333-40.

36. Schroeder C. [Use of electroencephalography in preeclampsia as means of predicting the onset of eclamptic convulsions.]. Med Welt. 1951 Mar 10;20:306-9.

37. Bork F. [Treatment of Severe Forms of Eclampsia.]. Dtsch Gesundheitsw. 1965 Mar 4;20:387-9.

38. Grimes DA, Ekbladh LE, McCartney WH. Cortical blindness in preeclampsia. Int J Gynaecol Obstet. 1980 May-Jun;17:601-3.

39. Grutzner A, Klees E. [Early diagnostic electroencephalography of focal cerebral changes in eclampsia.]. Gynaecologia. 1955 Feb;139:77-87.

40. Guieu JD, Milbled G, Pruvot P. [Electroencephalographic characteristics during a seizure of eclampsia]. Rev Electroencephalogr Neurophysiol Clin. 1975 Jul-Sep;5:267-9.

41. Leonardon N, Arfel G. [EEG discussions in a diagnosis of eclampsia]. Rev Electroencephalogr Neurophysiol Clin. 1975 Oct-Dec;5:420-5.

42. Marano E, Scuteri N, Vacca G, et al. HELLP syndrome with reversible posterior leukoencephalopathy. Neurol Sci. 2003 Jun;24:82-4.

43. Schroeder C, Heckel H. [The importance of electroencephalography for obstetrics and gynekology.]. Geburtshilfe Frauenheilkd. 1952 Apr;12:359-65.

44. Steiner GJ, Plasha MK. Late Postpartum Eclampsia: Report of a Case. Obstet Gynecol. 1964 Oct;24:594-6.

45. Thomas SV, Somanathan N, Radhakumari R. Interictal EEG changes in eclampsia. Electroencephalogr Clin Neurophysiol. 1995 Apr;94:271-5.

46. Iwanow IP. [Cerebrovascular disorders and their connection with the asymmetry of arterial pressure in pregnant women with late toxicosis]. Z Gesamte Inn Med. 1966 May 1;21:Suppl:83-5.

47. Moodley J, Bobat SM, Hoffman M, et al. Electroencephalogram and computerised cerebral tomography findings in eclampsia. Br J Obstet Gynaecol. 1993 Nov;100:984-8.

48. Sawhney IM, Subrahmanyan AV, Das CP, et al. Neurological complications of eclampsia. J Assoc Physicians India. 1999 Nov;47:1068-71.

49. Watson DL, Sibai BM, Shaver DC, et al. Late postpartum eclampsia: an update. South Med J. 1983 Dec;76:1487-9.

50. Aresin L. [Electroencephalographic studies in pregnancy toxemias.]. Z Geburtshilfe Gynakol. 1961 Nov;157:235-40.

51. Colle J, Janssens J, Renaer M, et al. [Electroencephalographic exploration in eclamptic diathesis.]. Brux Med. 1956 Nov 25;36:2295-304.

52. Ezes H, Mousseron C. [An attempt at the interpretation of the changes in electroencephalographic tracings observed in eclamptic patients.]. Rev Fr Gynecol Obstet. 1960 Dec;55:751-63.

53. Geiser-Rauch D. [Cardiazol-activated EEG in former eclampsia patients.]. Schweiz Med Wochenschr. 1958 Jul 12;88:683-6.

54. Janzen R, Schroeder C, Heckel H. [Eclampsia in the light of electroencephalographic investigations.]. Klin Wochenschr. 1952 Dec 1;30:1073-9.

55. Osmanagaoglu MA, Dinc G, Osmanagaoglu S, et al. Comparison of cerebral magnetic resonance and electroencephalogram findings in pre-eclamptic and eclamptic women. Aust N Z J Obstet Gynaecol. 2005 Oct;45:384-90.

56. ACOG Technical Bulletin. 1986, February.

57. Pritchard JA. Hypertensive disorders in pregnancy, Williams Obstetrics. In: Pritchard JA, PC MacDonald, editors. 16th ed. New York: Appleton-Century-Crofts; 1980. p. 665-700.

58. Deuschl G., Eisen A., editors. Recommendations for the practice of clinical neurophysiology: Guidelines of the international federation of clinical neurophysiology, Supplement 52 to Electroencephalography and Clinical Neurophisiology1999.

59. Tatum WOt, Husain AM, Benbadis SR, et al. Normal adult EEG and patterns of uncertain significance. J Clin Neurophysiol. 2006 Jun;23:194-207.

CHAPTER 3

Electroencephalography in normotensive and hypertensive pregnancies and subsequent quality of life

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Abstract

Objectives

To compare electroencephalography (EEG) findings during pregnancy and postpartum in women with normotensive pregnancies and pregnancies complicated by hypertensive disorders. Also the health related quality of life postpartum was related to these EEG findings.

Materials and Methods

An observational case-control study in a university hospital in the Netherlands. Twenty-nine normotensive and 58 hypertensive pregnant women were included. EEG's were recorded on several occasions during pregnancy and 6-8 weeks postpartum. Postpartum, the women filled out health related quality of life questionnaires. Main outcome measures were qualitative and quantitative assessments on EEG, multidimensional fatigue inventory, Short Form (36) Health Survey and EuroQoL visual analogue scale.

Results

In women with severe preeclampsia significantly lower alpha peak frequency, more delta and theta activity bilaterally and a higher EEG Sum Score were seen. Postpartum, these women showed impaired mental health, mental fatigue and social functioning, which could not be related to the EEG findings.

Conclusions

Severe preeclamptic patients show more EEG abnormalities and have impaired mental wellbeing postpartum, but these findings are not correlated.

Introduction

Preeclampsia (PE) is a multi-organ disease of unknown cause unique to human pregnancy. PE affects 1-7% of all pregnancies. Neurologic complications due to hypertensive disease in pregnancy are among the leading causes of maternal morbidity and mortality (1).

Currently we do not have a tool to monitor disturbances in the brain function in order to prevent complications. Electroencephalography (EEG) is known to be a sensitive method to detect brain dysfunction. EEG changes can be found before clinical symptoms are present and before ischemic conditions may result in irreversible brain dysfunction (2). We have published a systematic review on EEG in hypertensive pregnancy and believe there is need for new data, using the current terminology and definitions (3). The objective of this review was to evaluate the available medical literature concerning the EEG during hypertensive disorders of pregnancy. Abnormal EEG findings were observed in the majority of the women with PE/eclampsia, consisting of slow waves most frequently localized in the occipital lobe, as well as spike discharges. The EEG abnormalities in PE/eclampsia were reversible in the majority of the cases. We concluded that the described abnormalities might be interpreted as a warning sign of deterioration of brain function in PE/eclampsia. However, we advised some caution regarding this conclusion, because most of the retrieved articles were published in the 1950s and 1960s, and were not consistent with current clinical guidelines or medical terminology.

Somatic symptoms of PE, such as hypertension and proteinuria, generally disappear rapidly after delivery. However, formerly preeclamptic women more often complain of mental health problems as compared to women after uncomplicated pregnancies (4). These complaints may persist and can interfere with quality of life. Therefore, these complaints must not be underestimated.

We hypothesized that severe PE influences the brain through hypoxia and edema. This could therefore have an effect on brain function, which does not disappear immediately after delivery. This altered brain function could influence physical and mental health. In this study we describe EEG during the course of normotensive pregnancies as compared to hypertensive pregnancies and we relate EEG findings to health related quality of life (HRQoL) 6 to 8 weeks postpartum.

Materials and Methods

In this prospective longitudinal case-control study normotensive healthy pregnant women, serving as a control group, and patients with chronic hypertension (CH), pregnancy induced hypertension (PIH), mild preeclampsia (mild PE) and severe preeclampsia

(severe PE) underwent EEG testing during their pregnancies and postpartum. Postpartum all women filled out HRQoL questionnaires.

The Medical Ethics Committee Erasmus MC of Rotterdam approved the study protocol (MEC-2005-142). After obtaining written informed consent, participants were included in this study from October 2005 till October 2008.

Normotensive women, women with CH and women with PIH were consecutively recruited in the outpatient clinic. Patients with mild PE and severe PE were recruited after admission at the department of obstetrics of the Erasmus MC. Normotensive women and those with CH were examined at the following gestational ages: 12-14 weeks, 26-28 weeks, 32-34 weeks and 36-40 weeks. Women who developed PIH were included when diagnosed and examined at the same time points. Preeclamptic patients were consecutively included at admission and, if possible, measured weekly until delivery. Severely preeclamptic patients underwent an EEG after initial stabilization with antihypertensive medication and, if necessary, magnesium sulphate. Finally, all participants were re-examined 6-8 weeks postpartum. All participants spoke Dutch fluently. Exclusion criteria were: use of medication other than antihypertensive medication and/or magnesium sulphate, gestational diabetes, diabetes mellitus, pre-existing neurological disorders and psychiatric illnesses.

According to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP), PIH was defined as de novo hypertension after 20 weeks of gestation in absence of proteinuria and PE as hypertension in the presence of de novo proteinuria (5). Severe PE was diagnosed if in addition one or more of the following criteria were present: a systolic blood pressure of 160 mmHg or higher and/or a diastolic blood pressure of 110 mmHg or higher; proteinuria of 5 gram or more in a 24-hour urine specimen or dipstick urinalysis of 3+ or greater in two random urine samples collected at least 4 hours apart; oliguria of less than 500 mL in 24 hours; cerebral or visual disturbances; pulmonary oedema or cyanosis; epigastric or right upper-quadrant pain; impaired liver function; thrombocytopenia; foetal growth restriction (6). All patients who did not meet these criteria for severe PE were diagnosed as having mild PE.

Ethnicity and the level of education were obtained from the questionnaires. Level of education was assessed by the highest completed education. It was divided into three categories: low (primary school, lower vocational training and intermediate general school), mid (intermediate and higher vocational training) and high (university degree) (7).

The EEG recordings were made in accordance with the 10-20 International System of Electrode Placement. Electrode impedances were less than 5 kΩ (8). The registrations were recorded during wake. EEG registrations were blinded reviewed by one of the authors (GHV) using referential, source, and bipolar montages. In addition, the dominant occipital EEG activity (alpha rhythm) was quantitatively assessed using fast Fourier Transformation (FFT) and documented for both sides of the brain as alpha peak frequency (APF) (samples with epoch length 10 s; ≥ 10 epochs averaged). The EEG alpha

rhythm is electrical activity with an occipital maximum that can be seen in relaxed persons with eyes closed. In a healthy adult the normal frequency is above 8.5 Hz. Reference values of the APF are not gender specific and show a mean of 10.02 Hz (SD 0.9) (9). The visual assessment scored presence, type, amount and localization of intermittent slow activity, continuous slow activity, sharp waves and focal epileptiform activity. Delta waves are slow frequency waves present in deep sleep. Theta waves are slow frequency waves present just before sleep. We subdivide interictal findings in sharp waves and focal epileptiform activity. Sharp waves are associated with epileptic activity, but can also been found in people who never develop epileptic seizures. Focal epileptic activity always contains complexes with spikes and slow waves. Definitions of terms in interictal findings are published in Appendix S4 in Epilepsia (10). These activities were combined in the EEG Sum Score (Figure 1). This score was adapted from the Grand Total EEG score, which was published by Jonkman ranging from score 0 for a completely normal EEG to 17 for the most severely abnormal EEG (11, 12).

Alpha rhythm
1. Alpha peak frequency (APF) 0 = APF>9 Hz or APF is not measurable 1 = APF > 8 Hz and </= 9 Hz 2 = APF </= 8 Hz
Intermittent slow activity (theta or delta waves)
2. Presence 0 = none 1 = 1-10 times 2 = >10 times 3. Type 0 = theta and/or sporadic delta 1 = theta and delta 2 = mostly delta
Continuous slow activity (theta of delta activity)
4. Presence and type 0 = none 3 = theta and/or sporadic delta 5 = theta and delta or if mostly delta)
Sharp waves
5. Presence 0 = none 1 = 1-10 times 2 = >10 times
Focal epileptiform activity ((poly)spikes, (poly)spike-and-slow-wave complex)
6. Presence 0 = none 2 = 1-4 4 = >/=5 times

Figure 1. EEG Sum Score [a]

[a] EEG Sum Score is the sum of items 1 to 6, ranging 0-17 points

HRQoL is a multidimensional concept with physical, psychological and social domains. The combination of the domain-specific Multidimensional Fatigue Inventory (MFI) for fatigue and two generic measures of own health, Short Form (36) Health Survey (SF-36) and the EuroQoL visual analogue scale (EQ-VAS) classification, show good psychometric performance, are internationally standardized and widely used in the postpartum period (13-15).

For statistical analysis SPSS was used, version 20.0 (SPSS Inc. Chicago, Illinois, US). *P*-values < 0.05 were considered significant. The differences between the study groups on baseline characteristics and HRQoL were analysed using ANOVA, Pearson Chi-Square tests and Fisher's exact tests when applicable. ANCOVA was used to study the association of HRQoL with covariates. The correlation between the EEG items and HRQoL items was computed using the Spearman's correlation coefficient. To perform this analysis for the APF during pregnancy we used the area under the longitudinal trajectory of each patient as a summary of her APF profile (i.e., average APF during pregnancy). Postpartum we used the postpartum value of the APF. To account for the correlation in the repeated measurements of each patient during pregnancy, a repeated measures analysis has been performed to analyse each parameter using linear mixed effects models. Accordingly, for the Sum Score, a Poisson mixed effects regression was utilized. To allow for possible nonlinearities in the parameters' evolution in time we used regression splines of time in the specification of the fixed and random effects of the model, when supported from the data. The repeated measures analysis has been performed in the R statistical software (version 2.15.1) using package nlme (version 3.1-104). The models' assumptions were checked using residuals plots.

Results

A total of 103 pregnant women were initially included. Fifteen patients withdraw their participation after the first examination and one patient miscarried, remaining 87 study subjects: 29 normotensive women, nine CH, six PIH, 14 mild PE and 29 severe PE patients. Two of the previously normotensive pregnant patients developed PE (one mild PE and one severe PE) and one other patient developed PIH. They were categorized and analysed in the group with their contracted hypertensive disease. A total of 85 women received the HRQoL questionnaires, 71 questionnaires were returned. In 66 of those 71 cases an EEG was made postpartum.

Table 1 shows the patient characteristics. As expected, there are significant differences between the five groups in blood pressure, gestational age, mode of delivery and parity.

Table 1. Patient characteristics

Characteristics	Normotensive (n=29)	Chronic hypertension (n=9)	Pregnancy Induced Hypertension (n=6)	Mild Preeclampsia (n=14)	Severe Preeclampsia (n=29)	P value
Age (years) [a,b]	32.0 (5.3)	32.5 (3.2)	32.0 (5.1)	32.2 (4.5)	30.3 (6.5)	.687
Systolic blood pressure (mmHg) [a,b]	113 (12.1)*†‡	122 (16.5)*†	136 (16.9)	136 (10.2)	145 (16.8)	.000#
Diastolic blood pressure (mmHg) [a,b]	65 (7.1)*†‡§	78 (8.0)*†‡	87 (9.8)	87 (4.8)	92 (10.2)	.000#
Gestational age al delivery (days) [a,b]	277(11.5)*†	273 (12.3)*	266 (15.0)*	257 (19.4)*	224 (29.3)	.000#
Level of education [c,d]						.004#
Low	10.7	12.5	50	0	0	
Mid	60.7	75	16.7	92.9	85.2	
High	28.6	12.5	33.3	7.1	14.8	
Ethnicity [c,d]						.763
Caucasian	82.8	77.8	66.7	78.6	69.0	
Non-Caucasian	17.2	22.2	33.3	21.4	31	
Mode of delivery [c,d]						.000#
Vaginal	82.8	100	83.3	50.0	20.7	
Elective cesarean	13.8	0	16.7	21.4	75.9	
Emergency cesarean	3.4	0	0	28.6	3.4	
Parity [c,d]						.027#
Nulliparous	51.7	11.1	50.0	50	62.1	
Para-1	37.9	88.9	16.7	42.9	27.6	
Para-2	3.4	0	0	7.1	20.3	
Para-3	6.9	0	33.3	0	0	
NICU admission (days) [f]	0 (0-2)	0 (0-5)	0 (0-0)	2.5 (0-35)	13 (0-92)	.000#,e
Perinatal death [g]	0	0	0	0	1	

[a] Mean (SD)[b] One way ANOVA was used

[c] Number (%)

[d] Chi-Square test (Fisher's exact) was used

[e] Kruskal-Wallis test was used

[g] Median (range)

[f] Total

* p≤ 0.05 vs. sPE, †p≤ 0.05 vs. mPE, ‡p≤ 0.05 vs. PIH, §p≤ 0.05 vs. CH

p≤ 0.05

Abbreviations: NICU, Neonatal Intensive Care Unit; sPE, severe preeclampsia; mPE, mild preeclampsia; PIH, pregnancy induced hypertension; CH, Chronic Hypertension

Figure 2 presents APF during pregnancy and postpartum for each group. In 5 normotensive women, during one or more of the measurements, no alpha rhythm was detected and therefore APF could not be determined. In the groups with CH, PIH, mild PE and severe PE there were respectively 1, 0, 2 and 2 women where the APF could not be determined during one or more of the measurements. These measurements were excluded for APF analysis. The APF was measured occipital on the left and right side at every time point of the measurements. There was no significant left-right difference in APF in the normotensive group (Intraclass Correlation Coefficient of > 0.930 at all 5 time points). Therefore we used the mean of the right and left APF in further analysis. There was a strong intra-individual correlation between all subsequent time points (all pair wise r> 0.864, p< 0.001).

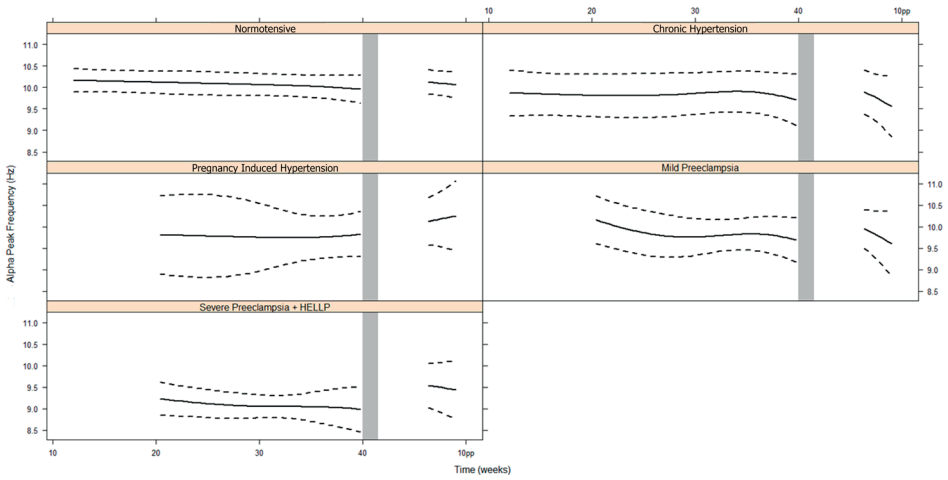

Figure 2. Alpha Peak Frequency during pregnancy and post partum [a]

[a] The repeated measures analysis has been performed using linear mixed effects models. Data are presented in mean and 95% Confidence Interval

Abbreviations: Hz, Hertz; pp, post partum, HELLP, Hemolysis Elevated Liver enzymes Low Platelets

We found no evidence of a time effect (Likelihood Ratio Test (LRT) = 13.5, degrees of freedom (d.f.) = 15, p = 0.560), meaning that the APF remained constant during pregnancy. However, there was an overall statistical difference between the five groups (LRT = 38.3, d.f. = 20, p= 0.008), but there was no indication that this difference attributed to differences in the longitudinal evolutions (LRT = 8.2, d.f. = 12, p= 0.770). The severe PE group differed significantly from the other groups (versus normal: p=0.000, versus CH: p=0.058, versus PIH: p=0.058, versus mild PE: p=0.007). The APF was on average 0.6 Hz higher postpartum than it was during pregnancy (p= 0.001) in all groups, but there were no significant differences between this increase and the absolute values postpartum (LRT = 2.6, d.f. = 4, p= 0.629).

There is no evidence of association between the mean APF and systolic blood pressure (p= 0.692), or between APF and diastolic blood pressure (p= 0.229). Repeated measures

ANOVA did not show a significant age-effect (p=0.191) or an effect of parity (p=0.500) on the APF values.

The amount, type and localization of EEG abnormalities are shown in Table 2. Per person more than one abnormality can be found. More intermittent slow and continuous slow activity was seen in the mild PE and severe PE groups, especially bilateral delta and theta activity fronto-temporal. In a few cases of severe PE sharp waves were seen and in one case epileptiform activity was seen postpartum. In the severe PE group abnormalities were more frequently. Because we did not find unilateral continuous slow activity and unilateral epileptiform activity, these activities were not included in Table 2.

Figure 3 presents the EEG Sum Score during pregnancy and postpartum for each group. We found no evidence of a time effect (LRT = 3.8, d.f. = 5, p= 0.581), meaning that the Sum Score also remained constant during pregnancy. There was an overall statistically significant difference between the five groups (LRT = 40.3, d.f. = 12, p<0.0001), but there was no indication that this difference attributed to the differences in the longitudinal evolutions (LRT = 2.8, d.f. = 4, p= 0.594). The severe PE group differed significantly from the other groups (versus normal: p=0.000, versus CH: p=0.027, versus PIH: p=0.005, versus mild PE: p=0.043). The mean Sum Score was on average 0.213 lower postpartum than it was during pregnancy and was not statistically different between the groups (p= 0.360). We did not find statistical differences between the study groups in the postpartum measurement of the EEG Sum Score (LRT = 3.2, d.f. = 4, p= 0.525). Furthermore, we found no evidence of an association between the EEG Sum Score and systolic blood pressure (p= 0.624) or diastolic blood pressure (p= 0.445).

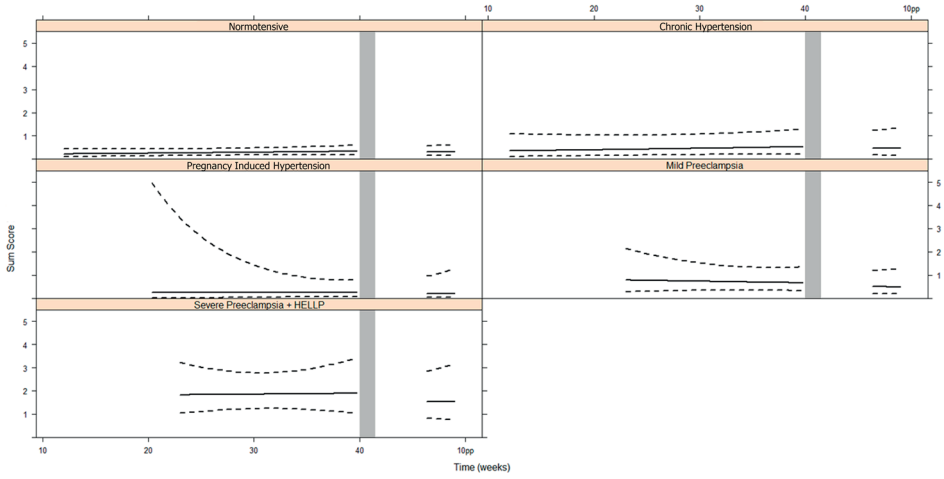

Figure 3. Sum Score during pregnancy and post partum [a]

[a] The repeated measures analysis has been performed using linear mixed effects models. Data are presented in mean and 95% Confidence Interval

Abbreviations: pp, post partum, HELLP, Hemolysis Elevated Liver enzymes Low Platelets

Table 2. Visually assessed EEG

Abnormal activity	**Normotensive**		**Chronic Hypertension**		**Pregnancy Induced Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**	
	Pregnancy (n=29)	Postpartum(n=27)	Pregnancy (n=9)	Postpartum (n=8)	Pregnancy (n=6)	Postpartum (n=6)	Pregnancy (n=14)	Postpartum (n=13)	Pregnancy (n=29)	Postpartum (n=25)
Intermittent slow activity [a]	8	7	2	3	1	0	5	3	16	15
Type										
Theta	5	5	1	2	0	0	1	2	8	7
Theta + sporadic delta	3	1	1	0	0	0	3	1	4	5
Theta + delta	0	1	0	1	1	0	1	0	4	2
Delta	0	0	0	0	0	0	0	0	0	1
Hemisphere										
Unilateral	1	1	0	1	0	0	0	0	0	0
Bilateral	7	6	2	2	1	0	5	3	16	15
Localization										
Diffuse	0	1	0	0	0	0	1	0	3	1
Focal	F=1,FT/T=7	FT/T=6	FT/T=2	FT/T=2,C/P=1	C/P =1	0	FT/T=4	FT/T=3	F=1,FT/ T=8,O=1	F=4,FT/ T=8,C/P=1
Multifocal	0	0	0	0	0	0	0	0	2	1
Continuous slow activity [a]	1	1	2	0	0	0	3	0	8	3
Type										
Theta	1	1	2	0	0	0	2	0	7	2
Theta +sporadic delta	0	0	0	0	0	0	1	0	0	1
Hemisphere										
Bilateral	1	1	2	0	0	0	3	0	7	3
Localization										
Diffuse	0	0	0	0	0	0	0	0	5	2

Table 2. Visually assessed EEG (continued)

Abnormal activity	**Normotensive**		**Chronic Hypertension**		**Pregnancy Induced Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**	
	Pregnancy (n=29)	Postpartum(n=27)	Pregnancy (n=9)	Postpartum (n=8)	Pregnancy (n=6)	Postpartum (n=6)	Pregnancy (n=14)	Postpartum (n=13)	Pregnancy (n=29)	Postpartum (n=25)
Focal	FT/T=1	0	FT/T=2	0	0	0	0	0	FT/T=1	FT/T=1
Multifocal	0	1	0	0	0	0	3	0	1	0
Focal sharp waves [a]	1	1	1	2	0	0	0	1	1	3
Hemisphere										
Unilateral	1	0	0	0	0	0	0	0	0	1
Bilateral	0	1	1	0	0	0	0	1	1	2
Localization										
Focal	FT/T=1	FT/T=1	FT/T=1	FT/T=2	0	0	0	FT/T=1	O=1	F=1,FT/T=2
Focal epileptiform activity [a]	0	0	0	0	0	0	0	0	0	1
Hemisphere										
Bilateral	0	0	0	0	0	0	0	0	0	1
Localization										
Focal	0	0	0	0	0	0	0	0	0	FT/T=1

[a] Total

Abbreviations: F, frontal; FT/T, fronto-temporal; C/P, central or parietal; O, occipital

In our study one woman in the normotensive group developed severe PE. Her individual APF values were plotted in Figure 4. She developed severe PE in the 38th week of gestation. This woman had a relatively low APF during her entire pregnancy and postpartum. The visual assessment of her EEG showed no anomalies, except at a gestational age of 35 weeks, as it showed focal bilateral intermittent theta and sporadic delta activity, which can be classified as mild and non-specific abnormalities. The other two normotensive women, who developed to PIH and mild PE, had APF values within the ranges of these groups.

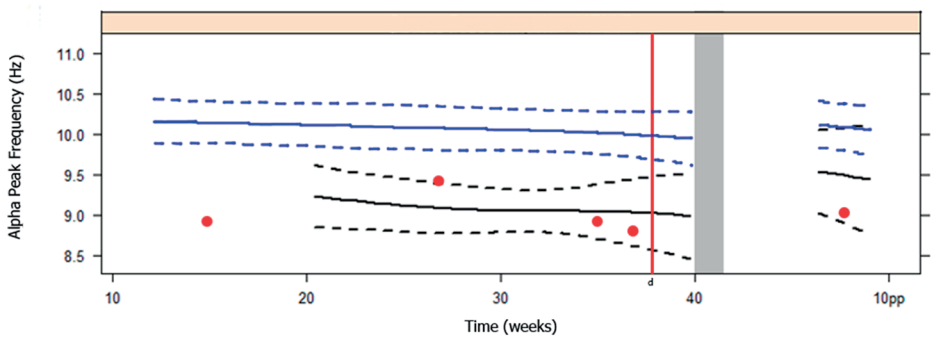

Figure 4. Course of Alpha Peak Frequency in a patient who developed Severe Preeclampsia [a,b,c]

[a] Data of patient is presented in red dots

[b] Black line and dotted lines are data of Severe Preeclampsia + HELLP, as presented in Figure 2

[c] Blue line and dotted lines are data of Normotensive women, as presented in Figure 2

[d] Red line: patient developed Severe Preeclampsia

Abbreviations: Hz, Hertz; pp, post partum; HELLP, Hemolysis Elevated Liver Enzymes Low Platelets

Table 3 shows the results of the HRQoL questionnaires (EQ-VAS, MFI and SF-36). Items reflecting mental health and fatigue, and social functioning were statistically different between the study groups. The patients with severe PE showed the worst HRQoL scores.

The internal consistency of the SF-36 and the MFI multi-item scales was determined with Cronbach's alpha-coefficient. The item General Health in the SF-36 had a Cronbach's alpha-coefficient of 0.51**,** due to the fact that the answers to some of the questions were given inconsistently. The other items had a Cronbach's alpha-coefficient of 0.70 or higher. Based on this, the internal consistency of the SF-36 and the MFI multi-item scales was considered sufficient for the purpose of group comparisons.

We investigated the association between the APF and EEG Sum Score values prior to delivery and postpartum with the HRQoL items measured postpartum. As a summary of the mean AFP during the course of pregnancy we used the area under the longitudinal trajectory of each patient. As a summary of the EEG Sum Score during the course of pregnancy we used the area under the longitudinal trajectory of each patient. The Spearman correlation coefficients between the summaries of the longitudinal trajectories and the postpartum HRQoL items, the APF values and EEG Sum Scores did not show any significant correlation.

Table 3. Results of EQ-VAS. MFI and SF-36

	Normotensive (n=25)	Chronic Hypertension (n=8)	Pregnancy Induced Hypertension (n=6)	Mild Preeclampsia (n=9)	Severe Preeclampsia (n=23)	Cronbach's alpha	P value a (unadjusted)	P value b (adjusted)
VAS (score 0-100) [c]	83.3 (10.7)*	85.3 (5.8)	84.3 (12.4)	81.7 (12.0)	76.5 (11.2)		0.165	0.294
MFI (score 4-20) [c]								
MFI total	47.6 (16.8)*	40.4 (14.6)*	42.5 (16.8)*	41.4 (11.1)*	57.3 (17.4)		0.038#	0.149
General Fatigue	11.8 (3.9)	10.5 (3.5)	11.5 (3.3)	11.6 (3.6)	13.3 (4.5)	0.86	0.465	0.740
Physical Fatigue	8.9 (4.5)	6.9 (2.5)*	10.0 (4.9)	8.6 (2.7)	10.9 (4.1)	0.89	0.149	0.429
Mental Fatigue	9.4 (4.3)*	8.6 (5.5)	6.8 (4.7)*	6.2 (2.1)*	12.0 (5.1)	0.92	0.012#	0.003#
Reduced Motivation	7.9 (4)	6.7 (2.2)	6 (2.5)*	7.1 (2.7)	9.4 (3.7)	0.80	0.137	0.248
Reduced Activity	9.6 (4.1)	7.6 (4.4)*	8.2 (5.1)	8.0 (3.2)*	11.3 (3.6)	0.83	0.097	0.402
SF-36 (score 0-100) [c]								
Physical Sum Score	51.0 (8.6)	52.0 (3.6)	46.3 (9.3)	50.7 (7.1)	47.9 (8.3)		0.455	0.638
Physical Functioning	87.1 (14.7)	93.0 (7.0)	80.0 (19.0)	95.0(5.0)	97.0 (10.5)	0.79	0.141	0.467
Role Physical	75.0 (36.9)	90.6 (26.5)	70.8 (33.2)	86.1 (33.3)	64.1 (36.0)	0.82	0.319	0.181
Bodily Pain	74.4 (30.9)	78.5 (29.7)	66.0 (28.5)	74.9 (29.8)	66.3 (30.8)	0.78	0.802	0.185
General Health	84.3 (13.4)*	82.0 (10.7)*	82.8 (13.9)*	79.3 (12.2)	70.4 (14.0)	0.51	0.010#	0.249
Mental Sum Score	50.4 (8.4)	56.5 (6.0)*	56.5 (5.3)*	55.6 (3.5)*	46.2 (10.7)		0.006#	0.020#
Vitality	60.2 (19.3)	73.6 (11.3)*	65.0 (21.7)	62.2 (16.0)	52.2 (19.2)	0.76	0.068	0.236
Social Functioning	78.5 (19.3)†§	95.3 (6.5)*	89.6 (12.3)*	93.1 (12.7)*	68.5 (21.6)	0.80	0.001#	0.022#
Role Emotional	83.3 (31.1)	98.5 (35.4)	94.4 (13.6)	96.3 (11.1)	72.5 (41.0)	0.84	0.326	0.153
Mental Health	78.7 (14.0)	90.5 (8.8)*	84.0 (16.0)	88.4 (8.6)*	72.7 (15.9)	0.75	0.008#	0.001#

[a] One way ANOVA was used

[b] ANCOVA was used to correct for maternal age, ethnicity, level of education, parity, gestational age and mode of delivery, and admission of the neonate at the NICU

[c] Mean (SD)

* p≤ 0.05 vs. sPE, †p≤ 0.05 vs. mPE, §p≤ 0.05 vs. CH

# p< 0.05

Abbreviations: NICU, Neonatal Intensive Care Unit; sPE, Severe Preeclampsia; mPE, Mild Preeclampsia; PIH, Pregnancy Induced Hypertension; CH, Chronic Hypertension

All items in Table 3 were tested for confounders. Differences between the study groups remained significant for the items mental fatigue (p=0.003), mental sum score (p=0.020), social functioning (p=0.022) and mental health (p=0.001) correcting for maternal age, ethnicity, level of education, parity, gestational age and mode of delivery, and admission of the neonate to the neonatal intensive care unit (NICU).

Discussion

This is the first longitudinal study on both quantitative and qualitative EEG findings in normotensive pregnant women and women with hypertensive disorders of pregnancy. In women with severe PE significantly lower APF, more bilateral delta and theta activity and a higher EEG Sum Scores were seen. These findings recovered postpartum. Postpartum, these women showed more impaired mental health, mental fatigue and decreased social functioning. These HRQoL outcomes, however, were not correlated with the above-mentioned EEG changes, as we hypothesized.

Our study shows that the APF remains constant during the course of pregnancy in all groups. In patients with severe PE the APF was significantly lower during the clinical phase of the disease. The APF was already altered during the non-clinical phase in the only normotensive patient that developed severe PE (Figure 4), but postpartum the APF remained low. The latter may be explained by a pre-existing phenomenon or by slow recovery from severe PE. Postpartum the differences in APF between the study groups disappeared, reflecting recovery of this aspect of brain function in severe PE patients. In only three patients with severe PE we recorded APF lower than 8.5 Hz during pregnancy. Postpartum, their APF measurements returned within the normal range. Low values in APF have also been found in patients with psychiatric disorders like depression, chronic fatigue syndrome and burnout.(16) A decrease in APF is related to decreased performance on memory tasks (17). In 2008 we published a study that showed that memory was impaired in formerly severe preeclamptic women (18).

We were not able to stratify for early (n=5) and late onset severe PE (n=24). In the subgroup of patients with early onset severe PE, APF was 0.8 Hz lower. However, this was not significant different, probably because of small sample size, but could be indicative for worse clinical disease. There were no significant differences in APF for the other hypertensive groups. The confidence intervals for the CH en PIH groups are wide (Figure 2), probably caused by the small sample size. We could not identify alpha rhythm during one or more of the sessions in 10 women (11.5%). In other studies the APF is poorly visualized in up to 25% of the general population due to inability to relax (19).

The EEG abnormalities found in normotensive pregnancies were mild, showing intermittent slow mostly theta activity and occasionally sharp waves, predominantly in the

frontal and temporal areas (Table 2). Focal epileptiform activity was not seen in the normotensive group. In women with abnormalities these were both seen during pregnancy and postpartum. In severe PE multifocal and bilateral intermittent and continuous slow activity was seen more frequently. Postpartum the decrease in continuous slow activity can be regarded as an improvement of the supposed hypertensive encephalopathy in these patients, although there was some increase in sharp waves and epileptiform activity. We can only speculate whether these abnormalities were already present before pregnancy, pregnancy induced, or will remain permanently. The EEG abnormalities found in this study might be reflected in cognitive failures like memory loss, as was earlier described (18, 20). Persistent cerebral anomalies were described in a MRI study in both formerly eclamptic and preeclamptic women with neurological symptoms and may actually reflect permanent brain ischemia (21). In our study EEG anomalies subsided or disappeared 6-8 weeks postpartum. EEG is in our opinion a more precise and sensitive instrument to detect functional brain damage than MRI.

In order to evaluate the visually assessed EEG in combination with the APF we summarized the EEG characteristics in the EEG Sum Score. This score did not significantly vary during the course of pregnancy and postpartum. Even the individual scores remained constant. This could either mean that the neuronal activity in the brain is not normalized completely 6 to 8 weeks postpartum, or is not influenced by pregnancy. Combining this finding with the results on APF, the first opinion is most likely.

We found in one third of the normotensive women (n= 9) that the EEG Sum Score was more than 0 during the first measurement, due to minor abnormalities in the visual assessment. Literature on EEG in normotensive pregnancies is scarce and relatively old (3). Two relatively small studies report EEG abnormalities in 15% of normotensive pregnant women (22, 23). Volume shifts, blood pressure and hormonal changes could be responsible. It's tempting to speculate that these minor EEG abnormalities reflect the often reported cognitive disturbances like mental slowness and forgetfulness during uneventful pregnancies.

The number of studies on the long term effects of PE is increasing (20, 24-26). As somatic symptoms merely disappear after delivery, many women continue to complain of cognitive disturbances. We showed that the severe PE group has the worst HRQoL scores, significantly in items reflecting mental fatigue, mental health and social functioning. These results are in line with other studies. Postpartum maternal morbidity after preeclamptic pregnancy may be directly related to the severity (27, 28). The psychosocial impact, admittance to an intensive care unit and health of the newborn may also affect women's mental health (24, 29, 30).

Lower APF and visual EEG abnormalities resulting in higher EEG Sum Score are mostly seen in the severe PE group during pregnancy. These abnormalities did not correlate

with worse HRQoL outcomes postpartum. Probably other, unknown, factors of the disease not evident in the EEG could have had more impact on HRQoL postpartum.

The strength of our study is the presence of longitudinal data on both quantitative and qualitative EEG findings during normotensive and hypertensive pregnancies, and postpartum. Another strength is that we quantified EEG data in APF and introduced the EEG Sum Score.

Due to the low incidence of preeclampsia a very large amount of normotensive women should be included to be able to perform EEGs systematically prior to the onset of PE. This can be seen as a limitation of our study. We chose to compare EEGs in a group of normotensive pregnant women to women with hypertensive disorders of pregnancy. Unfortunately, we included relatively small sample sizes in the groups of women with CH en PIH.

Our data can be used as reference values for EEGs performed during pregnancy and in the postpartum period. Preconception and late postpartum measurements are lacking which could be considered as a limitation, but logistically this was not possible.

This study adds knowledge of the reduced wellbeing that might be helpful in providing care for women after severe PE, which has consequences for their postpartum return to normal life and work.

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Literature

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631-44.
2. Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. J Clin Neurophysiol. 2004;21:341-52.
3. Brusse IA, Peters NC, Steegers EA, Duvekot JJ, Visser GH. Electroencephalography during normotensive and hypertensive pregnancy: a systematic review. Obstet Gynecol Surv. 2010;65:794-803.
4. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Steegers EA, et al. Poor health-related quality of life after severe preeclampsia. Birth. 2011;38:246-55.
5. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20:IX-XIV.
6. Bulletins--Obstetrics ACoP. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99:159-67.
7. Statistics Netherlands. Standard Classification of Education. Heerlen; Statistics Netherlands2003.
8. American Electroencephalographic Society guidelines for standard electrode position nomenclature. J Clin Neurophysiol. 1991;8:200-2.
9. Eeg-Olofsson O. The development of the electroencephalogram in normal adolescents from the age of 16 through 21 years. Neuropadiatrie. 1971;3:11-45.
10. Beniczky S, Aurlien H, Brogger JC, Fuglsang-Frederiksen A, Martins-da-Silva A, Trinka E, et al. Standardized computer-based organized reporting of EEG: SCORE. Epilepsia. 2013;54:1112-24.
11. Jonkman EJ. A simple scoring method for senile dementia of the Alzheimer type. Electroenceph Clin Neurophysiol. 1989;72:44p.
12. Claus JJ, Strijers RL, Jonkman EJ, Ongerboer de Visser BW, Jonker C, Walstra GJ, et al. The diagnostic value of electroencephalography in mild senile Alzheimer's disease. Clin Neurophysiol. 1999;110:825-32.
13. Jansen AJ, Duvekot JJ, Hop WC, Essink-Bot ML, Beckers EA, Karsdorp VH, et al. New insights into fatigue and health-related quality of life after delivery. Acta Obstet Gynecol Scand. 2007;86:579-84.
14. Jansen AJG, Essink-Bot M-L, Duvekot JJ, van Rhenen DJ. Psychometric evaluation of health-related quality of life measures in women after different types of delivery. Journal of Psychosomatic Research. 2007;63:275-81.
15. Prick BW, Steegers EA, Jansen AJ, Hop WC, Essink-Bot ML, Peters NC, et al. Well being of obstetric patients on minimal blood transfusions (WOMB trial). BMC Pregnancy Childbirth. 2010;10:83.
16. van Luijtelaar G, Verbraak M, van den Bunt M, Keijsers G, Arns M. EEG findings in burnout patients. J Neuropsychiatry Clin Neurosci. 2010;22:208-17.
17. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev. 1999;29:169-95.
18. Brussé IA, Duvekot JJ, Jongerling J, Steegers EAP, De Koning I. Impaired maternal cognitive functioning after pregnancies complicated by severe pre-eclampsia: a pilot case-control study. Acta Obstetricia et Gynecologica. 2008;87:408-12.

19. Tatum WOt, Husain AM, Benbadis SR, Kaplan PW. Normal adult EEG and patterns of uncertain significance. J Clin Neurophysiol. 2006;23:194-207.
20. Aukes AM, Wessel I, Dubois AM, Aarnoudse JG, Zeeman GG. Self-reported cognitive functioning in formerly eclamptic women. Am J Obstet Gynecol. 2007;197:365 e1-6.
21. Zeeman GG. Neurologic complications of pre-eclampsia. Semin Perinatol. 2009;33:166-72.
22. Poidevin LO. An electroencephalographic study of patients with toxaemia of pregnancy and controls. J Obstet Gynaecol Br Emp. 1955;62:417-20.
23. Sibai BM, Spinnato JA, Watson DL, Lewis JA, Anderson GD. Effect of magnesium sulfate on electroencephalographic findings in preeclampsia-eclampsia. Obstet Gynecol. 1984;64:261-6.
24. Cignacco E, Laederach-Hofmann K. [Pre-eclampsia and its psychosocial sequelae]. Schweiz Rundsch Med Prax. 1998;87:1019-23.
25. Roes EM, Raijmakers MTM, Schoonenberg M, Wanner N, Peters WHM, Steegers EAP. Physical well-being in women with a history of severe preeclampsia. The Journal of Maternal-Fetal and Neonatal Medicine. 2005;18:39–45.
26. Gaugler-Senden IP, Duivenvoorden HJ, Filius A, De Groot CJ, Steegers EA, Passchier J. Maternal psychosocial outcome after early onset preeclampsia and preterm birth. J Matern Fetal Neonatal Med. 2012;25:272-6.
27. Royburt M, Seidman DS, Serr DM, Mashiach S. Neurologic involvement in hypertensive disease of pregnancy. Obstet Gynecol Surv. 1991;46:656-64.
28. Weinstein L. Preeclampsia/eclampsia with hemolysis, elevated liver enzymes, and thrombocytopenia. Obstet Gynecol. 1985;66:657-60.
29. Meyer EC, Garcia Coll CT, Seifer R, Ramos A, Kilis E, Oh W. Psychological distress in mothers of preterm infants. J Dev Behav Pediatr. 1995;16:412-7.
30. Perrins J, King N, Collings J. Assessment of long-term psychological well-being following intensive care. Intensive Crit Care Nurs. 1998;14:108-16.

CHAPTER 4

Visual evoked potentials in normotensive and hypertensive pregnant women

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Submitted

Abstract

Objective

Preeclampsia is a severe hypertensive disorder of pregnancy which may lead to brain complications such as eclampsia. Visual symptoms are present in ~ 25% of preeclamptic women suggesting the visual cortex to be altered during preeclampsia. Visual evoked potentials (VEPs) measure the functional neuronal integrity of the visual pathway from retina to the occipital cortex of the brain. The objective of this study was to compare neurophysiological changes in women with hypertensive disorders of pregnancy using VEPs. We hypothesized that women with hypertensive disorders of pregnancy develop abnormal latency and amplitude of visual evoked potentials as compared to normotensive pregnant women.

Methods

We performed a prospective observational study in 29 normotensive pregnant women, 8 women with chronic hypertension, 9 with pregnancy- induced hypertension, 15 with mild preeclampsia and 33 with severe preeclampsia. VEP measurements were made at four different time points of gestation (12-14 weeks, 26-28 weeks, 32-34 weeks, 36-40 weeks) and 6-8 weeks postpartum.

Results

We defined reference values for normotensive pregnant women. Normotensive pregnant women had a shorter latency during pregnancy compared to their postpartum value ($P = 0.005$). Women with severe preeclampsia had a prolonged latency of VEPs compared to normotensive pregnant women ($P = 0.006$), a difference that disappeared postpartum.

Conclusions

Our study showed neurophysiological adaptation to pregnancy of the visual cortex in normotensive pregnant women, that seemed to be absent in women with hypertensive disorders of pregnancy.

Introduction

About 2-8% of all pregnancies are complicated by preeclampsia (PE), a major cause of morbidity and mortality in both mother and fetus (1, 2). The maternal brain can be involved in PE and lead to severe complications such as eclampsia (3, 4). Brain complications may be the result of a disturbed autoregulatory response of the brain to increased blood pressure and endothelial cell dysfunction, which clinically presents as posterior reversible encephalopathy syndrome (PRES) (5). An elevated cerebral perfusion pressure may also predispose to cerebrovascular complications in PE (6). In addition, abnormalities on the electroencephalogram (EEG) are observed during this disorder (4, 7). In fact, experimental PE is associated with neuroinflammation and significantly decreased seizure threshold (8). However, clinical evaluation of brain excitability during PE is not routinely performed that may help predict and/or prevent eclampsia in women with PE.

Visual symptoms are present in approximately 25% of pre-eclamptic women. The exact pathophysiology of this has not been elucidated yet. The origin of these visual disturbances may involve adaptation of the ophthalmic pathway (9). Normal pregnancy is associated with neurophysiological adaptations of the brain, including decreased inhibitory gamma-aminobutyric acid type A ($GABA_A$) receptor subunit expression in the cerebral cortex that lowers seizure threshold (10). In addition, a previous study showed visual evoked potential (VEP) latencies to decrease as gestation advances, suggesting adaptation of the visual cortex during pregnancy as well (11). However, the functional status of the visual cortex during PE or hypertension in pregnancy that could lead to visual symptoms has not been investigated.

The objective of this study was to compare neurophysiological function of the visual cortex using VEPs of normotensive pregnant women to women with hypertensive disorders of pregnancy. We studied women with mild and severe PE, women with chronic hypertension (CH) and pregnancy-induced hypertension (PIH). VEPs measure the functional integrity of the visual pathway from retina to the occipital cortex of the brain (12). The most clinically useful measurements are the latency and amplitude of the P100 component. Abnormal VEPs may present as changes in latency, amplitude, topography and waveform, of which latency prolongation is the most reliable parameter (13). Our hypothesis was that women with hypertensive disorders of pregnancy have an abnormal VEP latency and amplitude compared to normotensive pregnant women. In order to test this hypothesis longitudinally we studied these parameters during pregnancy and postpartum.

Materials and Methods

From October 2005 till July 2008 a prospective observational study was performed at the Department of Obstetrics and Gynecology of the Erasmus MC University Medical Center in the Netherlands. Approval for the study was given by the Erasmus MC, University Medical Centre Research Ethics Board (MEC 2005-142). All women provided written informed consent before participation. Normotensive and chronically hypertensive pregnant women were recruited at the outpatient clinic at a gestational age of 12 weeks. They underwent clinical and neurophysiological measurements at five different time points: at a gestational age of 12-14 weeks, 26-28 weeks, 32-34 weeks, 36-40 weeks and 6-8 weeks postpartum. Women with PIH or PE were recruited at the moment of diagnosis and investigated during remaining pregnancy and 6-8 weeks postpartum.

PE was defined as a systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥ 90 mmHg on at least two occasions 4 hours apart after 20 weeks of gestation or post-partum with proteinuria (≥ 300 mg/24 hours or protein/creatinine ratio ≥ 0.3 mg). Severe PE was defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥ 110 mmHg or PE with a multisystem complication (thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, cerebral disturbances, visual impairment) (14). Women with PE were treated with antihypertensive medication before the measurements. Women with gestational diabetes, diabetes mellitus, neurological disorders, muscular diseases and psychiatric disorders were excluded.

VEPs were measured using a Viking 4 device (Natus Neurology. Middleton, USA). We used pattern reversal stimulated VEPs because these responses show less individual variation and are more sensitive for lesions in the visual tract compared to flash VEP (12). The VEP recordings were made in accordance with the 10-20 International System of Electrode Placement (15). Briefly, the participant was instructed to focus on one central point in the pattern, while one eye was covered (Figure 1). The distance from eye to screen was 86 centimeters. The visual system was stimulated by a checkerboard pattern, which changes every half-second. The blocks were square, with a size of 1.5 cm. The total amount of illumination stayed the same. The time period of the analysis was 250 milliseconds following the onset of the visual stimulus. An average of at least 100 stimuli was produced and registered after two reproducible curves. All women had normal visual abilities (with or without correction) and normal electroretinogram, tested during the visit.

All data were analyzed using the statistical software package SPSS 21 (SPSS, Chicago, IL, USA). To test the clinical characteristics of the five study groups we used analysis of variance (ANOVA) and post hoc Dunnett t-test for pairwise comparisons or Kruskall-Wallis testing and post hoc Mann-Whitney testing for skewed data. Categorical data were compared using Chi-square/Fischer's exact testing. Comparisons of the VEP latency and

amplitude were made using an analysis of covariance (ANCOVA) model, adjusted for gestational age at measurement. The amplitude values were log transformed before testing because they were not normally distributed. VEP latency and amplitude were measured of the left and right eye of every woman (except for three women where only one side could be measured). Paired testing of the results of the VEP between both eyes showed no significant difference between the eyes. Consequently, the values used for the statistic model were randomly chosen. The reference value of VEP latency was determined by mean plus two standard deviations (latency upper limit). For VEP amplitude, which was not normally distributed, the 5th percentile was used as reference value (amplitude lower limit). A paired t-test was used for the comparison of the measurements during pregnancy with postpartum.

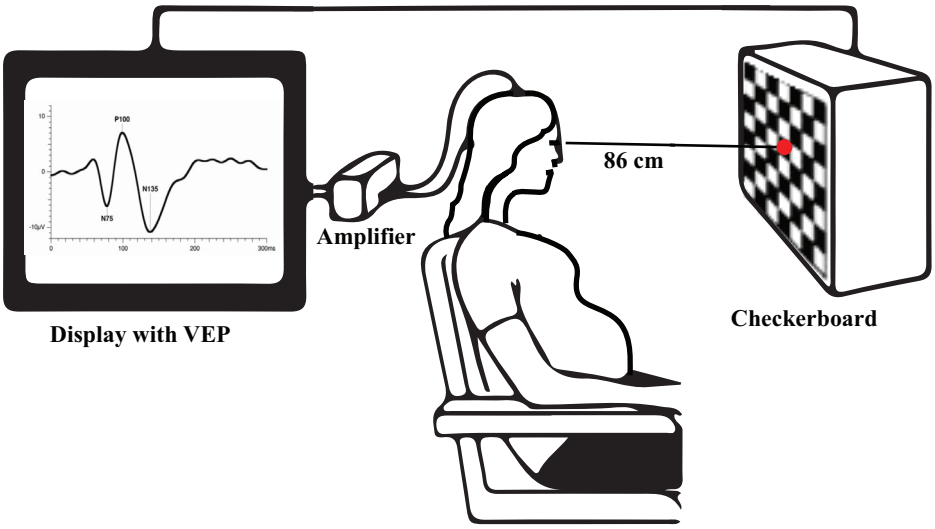

Figure 1. Image of a woman during VEP registration
Positions of the electrodes according to International 10-20 system: Oz (mid-occipital), O1 (occipital left hemisphere), O2 (occipital right hemisphere), T3 (temporal left hemisphere), T4 (temporal right hemisphere). Reference electrode Fz (mid-frontal). Earth electrode: Cz (mid-central).

Results

A total of 94 pregnant women participated in this study and underwent at least one VEP measurement. Twenty-nine women were normotensive, 8 had CH, 9 developed PIH, 15 mild PE and 33 severe PE. Clinical characteristics are shown in Table 1. Preconception BMI of the normotensive controls and women with severe PE was lower than the BMI of women with mild PE. As expected, gestational age at delivery was lower in the group

with severe PE compared to all other groups. Birth weight percentile was more often under the <10th percentile in mild and severe PE compared to normotensive controls. Multiple visual complaints were present in 18.8% of patients with severe PE and in 0% of normotensive pregnancies (table 1). We scored the following visual complaints: flashes, scotomas, blurry vision, blindness and disturbed color vision. Participants, who had more than one visual complaint, always reported flashes. Only severe PE patients reported more than two visual complaints.

Table 1. General characteristics

	Normotensive controls (n=29)	CH (n=8)	PIH (n=9)	mPE (n=15)	sPE (n=33)	P-value*
Demographics*						
Maternal age, years, mean (±SD)	32.0 (±5.3)	32.8 (±3.4)	32.7 (±5.6)	31.2 (±4.9)	30.0 (±6.7)	0.509
Ethnicity						0.819
Caucasian, n (%)	24 (82.8)	6 (75.0)	6 (66.7)	10 (66.7)	23 (69.7)	
Other, n (%)	5 (17.2)	2 (25.0)	3 (33.3)	5 (33.3)	9 (27.3)	
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	
Current pregnancy						
Nulliparous, n (%)	15 (51.7)	0 (0.0)	5 (55.6)	8 (53.3)	20 (60.6) [c]	0.033
Preconception BMI, kg/m^2 , median (IQR)	22.9 (21.1-26.6) [a]	28.5 (22.8-34.3)	28.5 (24.3-32.1)	29.7 (24.7-35.5)	23.2 (21.9-27.0) [a]	0.014
Preconception smoking, n (%)	8 (27.6)	0 (0.0)	2 (22.2)	1 (6.7)	5 (15.2)	0.292
Preconception alcohol, n (%)	11 (37.9)	1 (12.5)	1 (11.1)	3 (2.0)	5 (15.2)	0.267
Medical history						
Recurrent miscarriages, n (%)	0 (0.0)	1 (12.5)	1 (11.1)	1 (6.7)	1 (3.0)	0.190
PE in previous pregnancy, n (%)	0 (0.0) [c]	7 (87.5)	1 (11.1)	3 (20.0)	5 (15.2)	0.004
Refraction correction, n (%)	13 (44.8)	3 (37.5)	2 (22.2)	9 (60.0)	10 (30.3)	0.421
Visual complaints during pregnancy, n (%)[§]	0 (0%)	2 (25%)	1 (12.5%)	0 (0%)	6 (18.8%)	0.020

Table 1. General characteristics (continued)

	Normotensive controls (n=29)	CH (n=8)	PIH (n=9)	mPE (n=15)	sPE (n=33)	P-value*
Child characteristics						
Gestational age delivery, weeks, median (IQR)	40.0 (38.0-40.0) [b]	38.5 (37.0-40.0) [b]	38.0 (38.0-39.0) [b]	36.0 (33.0-37.0) [b]	31.0 (28.0-34.0)	<0.001
Birth weight, gram, median (IQR)	3600 (3600-3795) [a b]	3188 (2773-3785) [b]	3340 (3030-3565) [b]	2215 (1400-3150)	1225 (1010-2060)	<0.001
Birth weight percentile						<0.001
<10th percentile, n (%)	0 (0.0) [a b]	1 (12.5)	0 (0.0)	4 (26.7)	14 (42.4)	
10th-90th percentile, n (%)	22 (75.9)	6 (75.0)	8 (88.9)	11 (73.3)	19 (57,6)	
>90th percentile, n (%)	7 (24.1) [a]	1 (12.5)	1 (11.1)	0 (0.0)	0 (0.0%)	
Gender						0.804
Male, n (%)	15 (51.7)	4 (50.0)	4 (44.4)	10 (66.7)	16 (48.5)	
Female, n (%)	14 (43.8)	4 (50.0)	5 (55.6)	5 (33.3)	17 (51.5)	

* Categorical data are presented as n (%) with corresponding Chi^2/Fischer's exact testing. Continuous data are presented as a mean (standard deviation) or median (interquartile range) with corresponding ANOVA and post hoc Dunnett t-test for pairwise comparisons or Kruskall-Wallis testing and post hoc Mann-Whitney testing for skewed data. [a] p-value <0.05 versus mild PE pregnancies, [b] p-value <0.05 versus severe PE pregnancies, [c] p-value <0.05 versus CH. [§] More than 1 visual complaint including flashes, blurry vision, scotoma, blindness and disturbed color vision. NORM, normotensive pregnant women; CH, chronic hypertension; PIH, pregnancy induced hypertension; mPE, mild preeclampsia; sPE, severe preeclampsia

In Figure 2 individual values of VEP latency and amplitude throughout normotensive pregnancy is shown. There were no significant differences in mean latency and mean log transformed amplitude between the five groups by using ANCOVA models, adjusted for gestational age at measurement. Because only a limited number of women with hypertensive disorders were measured in the first and second trimester (only 9 women attended the first two visits) we were not able to analyze the data of these measurements longitudinally.

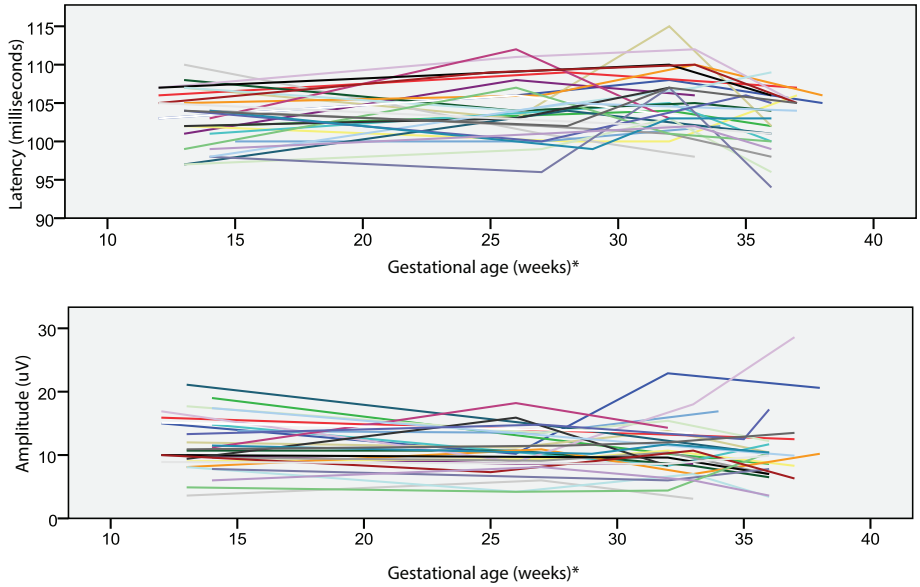

Figure 2. VEPs in normotensive pregnant women

* Each line represents the course of the VEP during the pregnancy of an individual study participant

The latency upper limit, determined in the group of normotensive pregnant women was 110 milliseconds (ms) during pregnancy and 113 ms postpartum. The amplitude lower limit values were 3.4 microvolts (µV) during pregnancy and 3.9 µV postpartum. Figure 3 shows individual VEP latencies of the women in relation to the upper limit, and individual VEP amplitudes of the women in relation to the lower limit. Table 2 shows the percentage of women with values above or below these limits. A higher percentage of women with severe PE had VEP latencies above the upper limit compared to normotensive pregnant women (29.4% versus 0%, P = 0.006). Six to eight weeks postpartum there were no differences remaining. Normotensive pregnant women showed a lower mean VEP latency during pregnancy compared to their postpartum value (Table 3; 102.89 ± 3.583 versus 104.86 ± 4.143, P = 0.005). In all other study groups there was no difference between the last measurement before delivery and the postpartum VEP value.

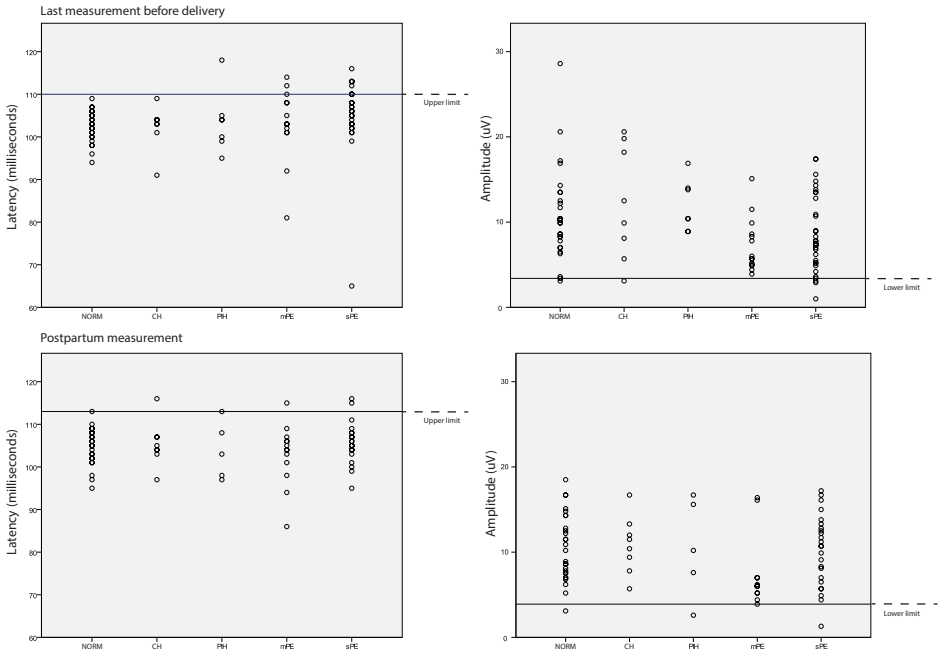

Figure 3. VEPs during pregnancy and postpartum

NORM, normotensive controls; CH, chronic hypertension; PIH, pregnancy induced hypertension; mPE, mild preeclampsia; sPE, severe preeclampsia. Latency upper limit: 110 milliseconds during pregnancy and 113 milliseconds postpartum; Amplitude lower limit: 3.4 μV during pregnancy and 3.9 μV postpartum

Table 2. Percentage of women with a VEP above the upper limit of latency or under the lower limit of amplitude

Latency					
Last measurement before delivery					
	NORM (n=29)	**CH (n=8)**	**PIH (n=7)**	**mPE (n=14)**	**sPE (n=34)**
≥110 ms	0 (0%)	0 (0%)	1 (14.3%)	3 (21.4%)	10 (29.4%)*
6-8 weeks postpartum					
	NORM (n=28)	**CH (n=8)**	**PIH (n=5)**	**mPE (n=13)**	**sPE (n=24)**
≥113 ms	1 (3.6%)	1 (12.5%)	1 (20%)	1 (7.7%)	2 (8.3%)
Amplitude					
Last measurement before delivery					
	NORM (n=29)	**CH (n=8)**	**PIH (n=7)**	**mPE (n=14)**	**sPE (n=34)**
<3.4 uV	1 (3.4%)	1 (12.5%)	0 (0%)	0 (0%)	3 (8.8%)
6-8 weeks postpartum					
	NORM (n=28)	**CH (n=8)**	**PIH (n=5)**	**mPE (n=13)**	**sPE (n=24)**
<3.9 uV	1 (3.6%)	0 (12.5%)	1 (20%)	0 (0%)	1 (4.2%)

*Significant difference from NORM group by using Fisher's Exact Test, P = 0.006

NORM, normotensive pregnant women; CH, chronic hypertension; PIH, pregnancy induced hypertension; mPE, mild preeclampsia; sPE, severe preeclampsia; ms, milliseconds; uV, microvolt.

Table 3. VEP latency (mean ± SD) and amplitude (ln(mean±SD)) during pregnancy and postpartum

Latency	**Last measurement before delivery**	**6-8 weeks postpartum**
NORM (n = 28)	102.89 ± 3.583	104.86 ± 4.143*
CH (n = 8)	102.38 ± 5.125	105.38 ± 5.317
PIH (n = 4)	104.25 ± 9.878	105.25 ± 6.850
mPE (n = 13)	102.69 ± 8.625	102.92 ± 7.182
sPE (n = 23)	104.87 ± 9.659	105.70 ± 4.656
Amplitude	**Last measurement before delivery**	**6-8 weeks postpartum**
NORM (n = 28)	2.26±0.41	2.27± 0.41
CH (n = 8)	2.34±0.67	2.34± 0.33
PIH (n = 4)	2.45±0.25	2.17± 0.75
mPE (n =13)	1.91±0.39	1.90± 0.43
sPE (n =23)	2.00±0.61	2.20± 0.57

*Significant different from last measurement before delivery by using paired T-test, P = 0.005.
NORM, normotensive controls; CH, chronic hypertension; PIH, pregnancy induced hypertension; mPE, mild preeclampsia; sPE, severe preeclampsia

Discussion

This is the first study to present VEP data in a relatively large group of pregnant women with and without hypertensive complications. Studying neurophysiological parameters may be useful in understanding the adaptation of the visual cortex to pregnancy and the impact of hypertensive disorders on this system that could contribute to visual symptoms.

VEP latency and amplitude did not change during the course of normotensive pregnancy. However, a higher percentage of women with severe PE had VEP latencies above the normal values whereas normotensive pregnant women had significantly shorter latencies during pregnancy compared to their postpartum measurements. These findings suggest one adaptation of the brain during normal pregnancy is to decrease VEP latency. This adaptation appears absent in women with hypertensive disorders of pregnancy.

Studies have previously shown that pregnancy is a state with higher neuronal network excitability and a lower seizure threshold (10, 16). However, other neurophysiological adaptations such as those occurring in the visual cortex are largely unknown.

Strength of this study is that we were able to retrieve a unique VEP dataset of normotensive pregnant women, which was collected longitudinally. This provided reference values in pregnancy. The VEPs were measured in a certified neurophysiological laboratory. Relatively large groups of women with mild and severe hypertensive disorders of pregnancy were included. A limitation of the study was that most women with severe PE delivered soon after recruitment and not all were able to participate in the postpartum measurement. This may be caused by the fact that most women with severe PE were

referred from other hospitals at a relatively large distance. Although we have data on all defined hypertensive disorders of pregnancy, including CH and PIH, we had very few cases in these groups. This made it difficult to draw any conclusions about women with CH and PIH. This also applies to the correlation of visual complaints with VEPs values, because of a lack of power.

There are few older studies available for VEP reference values in the literature. The guideline of the American Clinical Neurophysiological Society on VEP refers to older published work as well (13). One of those studies produced reference values in only 19 healthy volunteers of both sexes (17). Another study categorized their reference values for age and sex, but included only ten women in the group in the reproductive age (18).

A study in 1991 compared ten third trimester pregnant women to non-pregnant women and found reduced latencies in the pregnant women [18]. The authors concluded that normal pregnancy is a state that facilitates conduction process in the optic pathways (19). The results of this previous study support findings in the current study that normotensive pregnant women neurologically adapt to be more excitable. Normotensive pregnancy is associated with neurophysiological adaptations of the brain, including decreased inhibitory gamma-aminobutyric acid type A ($GABA_A$) receptor subunit expression in the cerebral cortex that lowers seizure threshold (8, 10, 20). This may be due to high levels of neurosteroids during pregnancy. The adaptation of the visual cortex has been studied during PE as well. Marsh *et al*. studied VEP in non-pregnant women, normotensive pregnant women and women with mild PE. This study found that normotensive pregnant women had a shorter VEP latency compared to non-pregnant women. They did not find differences in latency and amplitude for normotensive pregnant women compared to women with mild PE (11, 21). This finding is consistent with our finding that VEP latency only differed between normotensive pregnant women and women with severe PE.

In summary, we found that the visual cortex adapts neurophysiologically to normotensive pregnancy to have shorter latency of VEPs. This adaptation appears to be absent in women with hypertensive disorders of pregnancy, including PE. However, this adaptation can be assessed using neurophysiologic measurements including VEP.

Literature

1. Freathy RM, Mook-Kanamori DO, Sovio U, Prokopenko I, Timpson NJ, Berry DJ, et al. Variants in ADCY5 and near CCNL1 are associated with fetal growth and birth weight. Nat Genet. 2010;42(5):430-5.
2. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.
3. Duley L. The global impact of preeclampsia and eclampsia. Semin Perinatol. 2009;33(3):130-7.
4. Brusse IA, Peters NC, Steegers EA, Duvekot JJ, Visser GH. Electroencephalography during normotensive and hypertensive pregnancy: a systematic review. Obstet Gynecol Surv. 2010;65(12):794-803.
5. Narbone MC, Musolino R, Granata F, Mazzu I, Abbate M, Ferlazzo E. PRES: posterior or potentially reversible encephalopathy syndrome? Neurol Sci. 2006;27(3):187-9.
6. Sonneveld MJ, Brusse IA, Duvekot JJ, Steegers EA, Grune F, Visser GH. Cerebral perfusion pressure in women with preeclampsia is elevated even after treatment of elevated blood pressure. Acta Obstet Gynecol Scand. 2014;93(5):508-11.
7. Brusse IA, Duvekot JJ, Meester I, Jansen G, Rizopoulos D, Steegers EA, et al. Electroencephalography in Normotensive and Hypertensive Pregnancies and Subsequent Quality of Life. PLoS One. 2016;11(5):e0155299.
8. Johnson AC, Tremble SM, Chan SL, Moseley J, LaMarca B, Nagle KJ, et al. Magnesium sulfate treatment reverses seizure susceptibility and decreases neuroinflammation in a rat model of severe preeclampsia. PLoS One. 2014;9(11):e113670.
9. Roos NM, Wiegman MJ, Jansonius NM, Zeeman GG. Visual disturbances in (pre)eclampsia. Obstet Gynecol Surv. 2012;67(4):242-50.
10. Johnson AC, Nagle KJ, Tremble SM, Cipolla MJ. The Contribution of Normal Pregnancy to Eclampsia. PLoS One. 2015;10(7):e0133953.
11. Marsh MS, Smith S. Differences in the pattern visual evoked potential between pregnant and non-pregnant women. Electroencephalogr Clin Neurophysiol. 1994;92(2):102-6.
12. Creel D. Luminance-onset, pattern-onset and pattern-reversal evoked potentials in human albinos demonstrating visual system anomalies. J Biomed Eng. 1979;1(2):100-4.
13. American Clinical Neurophysiology S. Guideline 9B: Guidelines on visual evoked potentials. J Clin Neurophysiol. 2006;23(2):138-56.
14. Bulletins--Obstetrics ACoP. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99(1):159-67.
15. American Electroencephalographic Society guidelines for writing clinical evoked potential reports. J Clin Neurophysiol. 1991;8(1):85-7.
16. Johnson AC, Cipolla MJ. The cerebral circulation during pregnancy: adapting to preserve normalcy. Physiology (Bethesda). 2015;30(2):139-47.
17. Hughes JR, Stone JL, Fino JJ, Hart LA. Usefulness of different stimuli in visual evoked potentials. Neurology. 1987;37(4):656-62.
18. Kjaer M. Visual evoked potentials in normal subjects and patients with multiple sclerosis. Acta Neurol Scand. 1980;62(1):1-13.

19. Tandon OP, Bhatia S. Visual evoked potential responses in pregnant women. Indian J Physiol Pharmacol. 1991;35(4):263-5.

20. Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci. 2009;29(30):9592-601.

21. Marsh MS, Smith S. The visual evoked potential in the assessment of central nervous system effects of pre-eclampsia: a pilot study. Br J Obstet Gynaecol. 1994;101(4):343-6.

CHAPTER 5

Cerebral perfusion pressure in preeclamptic patients is elevated even after treatment of elevated blood pressure

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Abstract

Cerebral perfusion pressure (CPP) is elevated in preeclampsia, and may predispose to cerebrovascular complications and progression to eclampsia. We estimated zero flow pressure (ZFP) and CPP using simultaneously obtained arterial blood pressure and middle cerebral artery blood flow velocity in 10 preeclamptic women, all treated with methyldopa ± nifedipine, and 18 healthy pregnant controls. Mean±SD ZFP was lower in patients than in controls (16.8±10.9 versus 31.7±15.0 mmHg,p=0.01) whereas CPP was considerably higher (82.3±17.7 versus 55.0±11.7 mmHg,p<0.001), as was the cerebral flow index (41.9±18.0 versus 25.6±11.2,p=0.02). There was a significant correlation between blood pressure and CPP in patients with preeclampsia, but not in controls. Preeclamptic women may have an increased cerebral perfusion due to a reduced ZFP and increased CPP despite treatment with antihypertensive medication. More rigorous antihypertensive therapy, aimed at reducing CPP, could result in a decrease in cerebral complications in preeclamptic patients.

Introduction

Preeclampsia complicates 3% of pregnancies and is a major cause of maternal and foetal morbidity and mortality (1). Cerebral infarction and haemorrhage account for the majority of maternal deaths from preeclampsia. The pathophysiology of cerebral damage in preeclampsia is unclear, but recent studies conducted with MRI have shown an increased cerebral blood flow in preeclamptic patients (2), and Belfort *et al.* reported patients with severe preeclampsia have an increased cerebral perfusion pressure (CPP) (3). High CPP was also shown to be associated with preeclampsia related symptoms such as headache, and has also been reported in patients who subsequently developed eclamptic seizures.

Currently used drugs in patients with preeclampsia, such as labetalol and $MgSO_4$, tend to lower CPP, while nimodipine is associated with a mild increase. Furthermore, a randomized study in preeclamptic patients reported that therapy with nimodipine is associated with more frequent eclamptic seizures in comparison with $MgSO_4$ (4). These findings may be explained by the different effects of these drugs on CPP.

We aimed to investigate whether CPP, as estimated using simultaneously measured arterial blood pressure (ABP) and middle cerebral artery blood flow velocity (V_{mca}), is elevated in preeclamptic patients, in whom blood pressure is adequately treated with antihypertensive medication.

Material and Methods

After obtaining informed consent, 10 preeclamptic patients and 18 healthy pregnant controls, admitted to the department of obstetrics of the Erasmus Medical Center, University Medical Center Rotterdam, were consecutively enrolled in this study. Preeclampsia was diagnosed according to the definition of the International Society for the Study of Hypertension in Pregnancy (ISSHP) (5). Preeclampsia was diagnosed as: hypertension in the presence of de novo proteinuria (5). Severe preeclampsia was diagnosed if one or more of the following criteria were present: blood pressure of ≥160 mmHg systolic or ≥110 mmHg diastolic on two occasions at least 6 hours apart; proteinuria of 5 gram or more in a 24-hour urine specimen or dipstick urinalysis of 3+ or greater in two random urine samples collected at least 4 hours apart; oliguria of less than 500 mL in 24 hours; cerebral or visual disturbances; pulmonary edema or cyanosis; epigastric or right upper-quadrant pain; impaired liver function; thrombocytopenia; fetal growth restriction (5). Exclusion criteria for this study were cerebral vascular disorders, diabetes mellitus, pre-existing hypertension and inadequate language skills. The study protocol was approved by the Institutional Review Board of the Erasmus MC University Medical Center Rotterdam.

Transcranial Doppler measurements of the middle cerebral artery flow velocity (V_{MCA}) were conducted using a Digi-Lite monitoring system (RIMED, Jerusalem, Israel) using a 2 MHz probe after identification using the imaging feature. Mean V_{MCA} was estimated as a weighted mean velocity. ABP was continuously measured non-invasively using a Finometer Midi (Finapres Medical Systems, Amsterdam, the Netherlands). The Finometer Midi allows for easy, non-invasive measurement of ABP using a finger cuff with a mounted infrared plethysmograph (6). Expired CO_2 was measured using the Capnomac Ultima.

The zero-flow pressure (ZFP) in the circulation is the arterial pressure at which flow ceases. Dynamic pressure-flow-plots of the ABP and V_{MCA} have been used to extrapolate the ZFP of the cerebral circulation (7, 8). During measurement sessions, a 2 to 5 minute time interval with stable measurements was specified on the case record form. For our analysis we used systolic and diastolic values from up to 10 pulse waves (two respiratory cycles) to minimize the effect of breathing. ZFP was subsequently extrapolated by linear regression analysis through the individual measurements (figure 1). The CPP was calculated as the difference between weighted mean ABP (MAP) and ZFP. CPP was also calculated using a formula proposed by Belfort et al(3): CPP = (meanV_{MCA}/(mean V_{MCA}-diastolic V_{MCA})) x(mean ABP-diastolic ABP). Resistance area product (RAP) is an index of cerebrovascular resistance is obtained by dividing MAP by the mean V_{MCA}. Cerebral Flow Index (CFI), an index of total cerebral blood flow (CBF), was calculated as CFI = CPP / RAP (3).

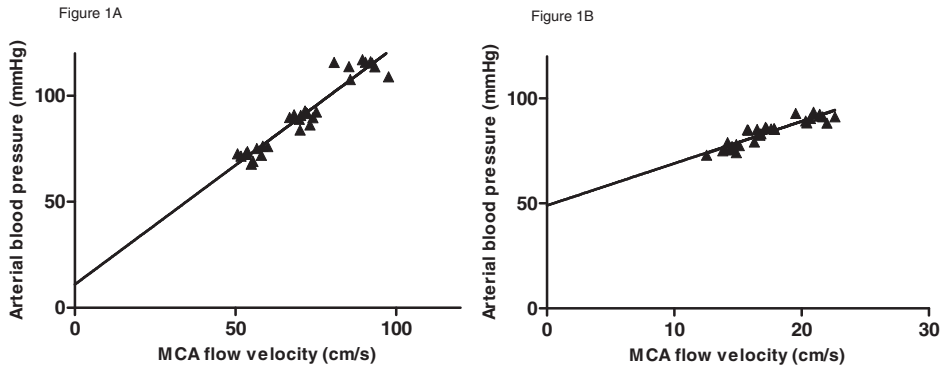


Figure 1A and 1B

Estimation of the ZFP by extrapolation of simultaneously measured beat-by-beat data on arterial blood pressure (systole and diastole) and middle cerebral artery blood flow velocity in a case (A) and a control (B)

SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Results of continuous variables are presented as mean ± SD and results between groups were compared using t-tests and chi-square tests. All statistical tests were two-sided and were evaluated at the 0.05 level of significance. The study protocol (MEC-2008-035) was approved by the Institutional Review Board of the Erasmus MC University Medical Center on April 29th 2008

Results

Age, parity and gestational age at inclusion were similar between patients and controls (Table 1). Five patients had severe preeclampsia. All patients were treated with methyldopa; three patients received a combination of methyldopa with nifedipine. One of the patients smoked during pregnancy, including the day that the measurements were performed, compared to none of the controls. None of the patients developed complications during follow-up. Gestational age at delivery for cases and controls was 32 ± 4.9 versus 37.4 ± 3.4 weeks (p=0.012). Patients with preeclampsia had higher ABP and V_{MCA} than controls (Table 1). End-tidal CO_2 did not differ between cases and controls (41.15 ± 2.52 versus 41.63 ± 2.97 mmHg, p=0.699). Pulsatility indices of the MCA were 0.47 and 0.40 in cases and controls (p=0.23).

Table 1. A comparison of characteristics and measurements between cases and controls.

Patient characteristics	Patients (n=10)	Controls (n=18)	P-value
Demographics			
Age (years)	29.9 (2.3)	32.4 (6.4)	0.14
Nulliparous	7 (70%)	10 (56%)	0.51
Severe pre-eclampsia	5 (50%)	-	
Gestational age at examination (weeks)	30.4 (3.2)	32.1 (3.2)	0.18
Gestational age at delivery (weeks)	32.3 (4.9)	37.4 (3.4)	0.012
Blood pressure (mmHg)			
Systolic	123.8 (12.7)	101.5 (12.3)	<0.001
Mean	99.1 (9.1)	86.7 (9.3)	0.002
Diastolic	84.2 (7.7)	78.2 (10.3)	0.12
MCA flow velocity (cm/s)			
Systolic	65.4 (25.0)	49.2 (17.2)	0.05
Mean	50.7 (19.6)	38.8 (13.5)	0.07
Diastolic	41.5 (15.8)	33.8 (12.3)	0.16
Cerebral Perfusion			
Zero Flow Pressure (mmHg)	16.8 (10.9)	31.7 (15.0)	0.01
Cerebral Perfusion Pressure (mmHg)	82.3 (17.7)	55.0 (11.7)	<0.001
Cerebral Flow Index	41.9 (18.0)	25.6 (11.2)	0.02
Resistance Area Product	2.30 (1.21)	2.54 (1.04)	0.583

Mean levels of blood pressure, middle cerebral artery flow velocity, zero flow pressure, cerebral perfusion pressure and cerebral flow index. MCA, middle cerebral artery. Standard deviations are shown in brackets.

Extrapolated ZFP was 16.8 ± 10.9 mmHg in preeclamptic women, compared to 31.7 ± 15.0 mmHg in controls (p=0.01). Estimated CPP was 82.3 ± 17.7 mmHg in patients compared to 55.0 ± 11.7 mmHg in controls (p<0.001). Consequently, preeclamptic patients had a higher CFI than controls (41.9 ± 18.0 versus 25.6 ± 11.2, p=0.02). We have also calculated CPP using the method as proposed by Belfort et al. (3): the two measures of CPP are highly correlated (r=0.659, p=0.001). Patients also tended to have higher CPP than controls when estimated using the Belfort method: 87.1 ± 26.3 vs 70.7 ± 22.1 mmHg (p=0.09).

In a multivariate regression model adjusting for parity, gestational age at time of measurement and age at enrolment, patients with preeclampsia had higher CPP both when calculated using the regression method (adjusted CPP 83.2 versus 54.5 mmHg, p<0.001) and the Belfort method (adjusted CPP 86.1 versus 69.6 mmHg, p=0.036).

In controls, there was no correlation between mean ABP and CPP (r=-0.004, p=0.99), but in patients a distinct correlation was found between these parameters (r=0.859, p=0.001).

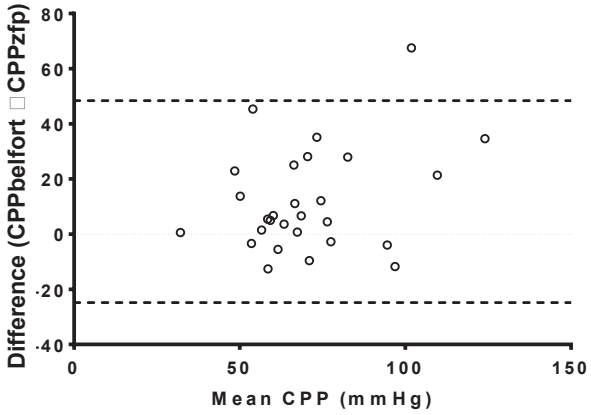
Discussion

The Dutch Maternal Mortality Committee reported cerebrovascular complications to be the major cause of death in hypertensive pregnant women (9). Increased CPP has been implicated as a possible mechanism to induce a cerebral hyperperfusion syndrome and subsequent cerebrovascular complications in preeclamptic patients (2, 3). The CPP in our healthy control group compares well with those from other reports, including a large study by Belfort et al (10). In the current study, we found that CPP was elevated in preeclamptic patients after adequate treatment with antihypertensive therapy. Interestingly, this increase seems to be dependent upon a decrease in ZFP, as opposed to being only an effect of the difference in blood pressure between patients and controls. The ZFP we found for healthy pregnant controls is compatible with earlier reports (11), but whereas Sherman *et al.* found an increased ZFP in their population of untreated preeclamptics, we found a thoroughly decreased level in our study. A possible explanation for this discrepancy is the effect of medication on the ZFP: while the antihypertensive agents lowered blood pressure, other cerebrovascular mechanisms may have been induced that lowered ZFP, thereby maintaining an elevated cerebral perfusion pressure (11). In our study we used methyldopa and nifedipine to lower blood pressure.

CPP in patients with preeclampsia strongly correlates with ABP whereas this correlation is absent in healthy pregnant controls. The elevated CPP was also accompanied by an increase in V_{mca} and CFI. Under normal circumstances, cerebrovascular autoregulation would maintain a stable cerebral blood flow, using cerebral vasoconstriction and a sub-

sequent change in ZFP, in the face of changes in the systemic circulation. Our findings therefore allude to a possible loss of cerebral autoregulation in preeclamptic patients.

A limitation of our study is that we used non-invasive methods for estimation of ZFP and CPP. These methods have not been validated in vivo in humans. Given these limitations, we have chosen to use the two most often applied methods for estimation of CPP and show that our findings are consistent irrespective of the method used, despite varying estimates observed across the methods (supplementary figure 1). The reason for the variation is currently unclear, and requires further investigation. Also, preeclamptics had a higher ABP than did the controls, despite antihypertensive therapy. This is in line with current treatment guidelines and therefore reflects clinical practice (12).



Supplementary figure 1.
Bland-Altman comparison of the two methods for cerebral perfusion pressure estimation. Bold dashed lines represent the 95% confidence limits for the difference.

In conclusion, the current study shows that in preeclamptic patients treated with antihypertensive therapy to reduce systolic ABP to <140 mmHg, in line with international and Dutch guidelines, CPP and consequently cerebral perfusion are elevated. Possibly, more rigorous antihypertensive therapy, aimed at reducing CPP, could therefore result in a decrease in cerebral complications in these patients although further studies are required to confirm this hypothesis. Future studies on elevated blood pressure control in preeclampsia should investigate the effect of reducing CPP on the risk of cerebral complications in preeclampsia.

Literature

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 376:631-44.
2. Zeeman GG, Hatab MR, Twickler DM. Increased cerebral blood flow in preeclampsia with magnetic resonance imaging. Am J Obstet Gynecol. 2004;191:1425-9.
3. Belfort MA, Varner MW, Dizon-Townson DS, Grunewald C, Nisell H. Cerebral perfusion pressure, and not cerebral blood flow, may be the critical determinant of intracranial injury in preeclampsia: a new hypothesis. Am J Obstet Gynecol. 2002;187:626-34.
4. Belfort MA, Anthony J, Saade GR, Allen JC, Jr., Nimodipine Study G. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med. 2003;348:304-11.
5. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20:IX-XIV.
6. Guelen I, Westerhof BE, van der Sar GL, van Montfrans GA, Kiemeneij F, Wesseling KH, et al. Validation of brachial artery pressure reconstruction from finger arterial pressure. Journal of hypertension. 2008;26:1321-7.
7. Kalmar AF, Dewaele F, Foubert L, Hendrickx JF, Heeremans EH, Struys MM, et al. Cerebral haemodynamic physiology during steep Trendelenburg position and CO(2) pneumoperitoneum. Br J Anaesth. 2012;108:478-84.
8. Panerai RB. The critical closing pressure of the cerebral circulation. Med Eng Phys. 2003;25:621-32.
9. Schutte JM, Schuitemaker NW, van Roosmalen J, Steegers EA, Dutch Maternal Mortality C. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. Bjog. 2008;115:732-6.
10. Belfort MA, Tooke-Miller C, Allen JC, Jr., Saade GR, Dildy GA, Grunewald C, et al. Changes in flow velocity, resistance indices, and cerebral perfusion pressure in the maternal middle cerebral artery distribution during normal pregnancy. Acta Obstet Gynecol Scand. 2001;80:104-12.
11. Sherman RW, Bowie RA, Henfrey MM, Mahajan RP, Bogod D. Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography. Br J Anaesth. 2002;89:687-92.
12. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2002;77:67-75.

CHAPTER 6

Electromyographically recorded patellar reflex in normotensive pregnant women and patients with preeclampsia

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Abstract

Objective
To define reference values of the patellar reflex in normotensive pregnant and postpartum women and to compare these with values in women with preeclampsia.

Design
Observational study.

Setting
University teaching hospital in the Netherlands.

Population
Normotensive non-pregnant women, pregnant women and preeclamptic women.

Methods
In normotensive pregnant women the patellar reflex was cross-sectionally recorded using surface electromyography at four time points during pregnancy and 6-8 weeks postpartum. In non-pregnant normotensive women this was recorded once. Preeclamptic women were recorded during pregnancy and postpartum.

Main outcome measures
Latency and amplitude of the compound muscle action potential of the patellar reflex.

Results
Latency and amplitude of the compound muscle action potential during normotensive pregnancies showed no changes compared to the non-pregnant state during reproductive age. Latency of the compound muscle action potential was increased in pregnancies with severe preeclampsia compared to normotensive pregnancies. Postpartum these differences had disappeared.

Conclusions
During pregnancy, the patellar reflex can be assessed using surface electromyography. Latency and amplitude show no changes during normotensive pregnancies and are no different from the postpartum or non-pregnant values. In severe preeclamptic women latency is increased. The clinical value of the latter is limited.

Introduction

Preeclampsia and eclampsia are hypertensive disorders of pregnancy that may be accompanied by clinical symptoms of hyperexcitability and cerebral complications. In obstetric clinical practice, the patellar reflex is often used in the assessment of preeclamptic patients and is believed to predict the risk of an eclamptic fit. The risk of an eclamptic fit is thought to correlate with the briskness or augmentation of the tendon reflexes. The impression of hyperreflexia is determined by the visual outcome of the patellar reflex, which is reflected by the amplitude of the compound muscle action potential (CMAP). The clinical management is based on this visual assessment. However, there is large inter-observer variability in the semi-quantitative assessment of the routine patellar reflex results (1). This semi-quantitative assessment involves a five- to nine-point scoring scale, which assesses the amplitude of the reflex visually. The latency (time delay from stimulus to the onset of the CMAP) of the reflex cannot be assessed with this subjective method. Moreover, the inter-observer variability is likely to be larger during bedside assessment compared to the assessment in a study. To reduce inter-observer disagreement, the patellar reflex can be objectively quantified by surface electromyography (SEMG) (2). This method measures quantitatively the evoked CMAP of a muscle which reflex is initiated. CMAP can be documented as latency and amplitude of the resulting electrical wave form (Figure 1).

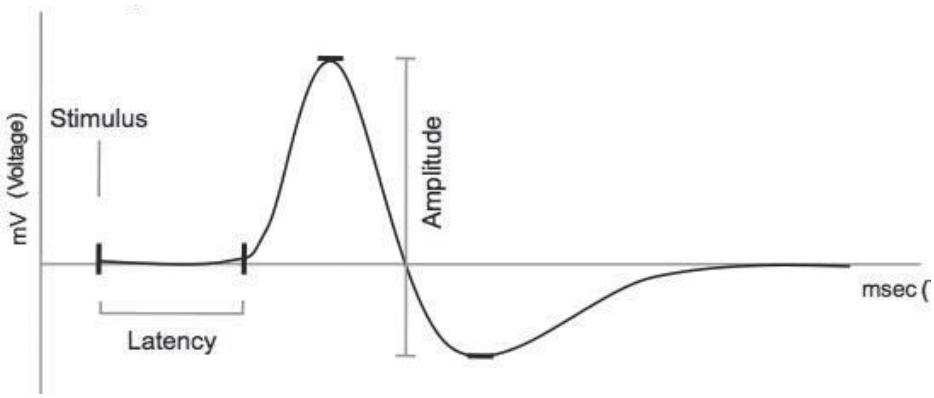

Figure 1. An example of a compound muscle action potential of the patellar reflex.

To date, there are only four publications on normative EMG (electromyography) data of the patellar reflex, none of which were conducted during pregnancy and only one examined the vastus medialis muscle (3-6). The first purpose of the present study was to define reference values of the CMAP of the vastus medialis muscle in healthy pregnant women using SEMG and to determine whether the patellar reflex is affected by normo-

tensive pregnancy. Secondly, we compared these results of normotensive pregnancies with those in pregnancies with preeclampsia.

Material and Methods

In this prospective cross-sectional study, normotensive non-pregnant women of reproductive age, normotensive pregnant women and preeclamptic women were recruited from the Department of Obstetrics and Gynecology of the Erasmus MC University Medical Center, in the Netherlands from October 2005 till July 2008. Normotensive non-pregnant women were mostly students, workers in the university and university hospital. Normotensive pregnant women were out-patients. Preeclamptic women were admitted and treated for their raised blood pressure before the measurements. The medical ethics committee of the Erasmus MC approved the study and all participants provided written informed consent (MEC-2005-142).

In normotensive pregnant women the patellar reflex was cross-sectionally recorded using SEMG at four time points during the following gestational age periods: 12-14 weeks, 26-28 weeks, 32-34 weeks, 36-40 weeks and 6-8 weeks postpartum. In non-pregnant normotensive women the patellar reflex was recorded once. Recordings from preeclamptic women were obtained during pregnancy and 6-8 weeks postpartum.

Preeclamptic women were divided into a mild and severe group according to the American Congress of Obstetricians and Gynecologists (ACOG) criteria (7). Severe preeclampsia was diagnosed if in addition one or more of the following criteria were present: a blood pressure of ≥160 mmHg systolic or ≥110 mmHg diastolic on two occasions at least six hours apart; proteinuria of ≥5g in a 24-hour urine specimen or dipstick urinalysis of ≥3+ in two random urine samples collected at least four hours apart; oliguria of <500 mL in 24 hours; cerebral or visual disturbances; pulmonary edema or cyanosis; epigastric or right upper-quadrant pain; impaired liver function; thrombocytopenia; fetal growth restriction. Antihypertensive medication (methyldopa, labetolol, nifidipine, nicardipine) and magnesium sulphate was used according to international guidelines (8). Exclusion criteria were: use of contraceptive medication (non-pregnant women), gestational diabetes, diabetes mellitus, neurological disorders, muscular diseases and psychiatric disorders.

Patellar reflexes were recorded in all participants using a Viking III P EMG device (Nicolet, Madison, Wisconsin, USA). Surface electrodes were used to record the CMAP. The negative electrode was placed over the muscle belly of the vastus medialis muscle (Figure 2). The positive electrode was placed on the patella. The ground electrode was placed laterally just above the knee. The reflex was initiated using a triggering reflex hammer wired to the EMG device. It was initiated ten times, in order to reduce influential factors, like inaccurate hammering of the patellar tendon and short time fluctuations of

central inhibition of the reflex. The women were positioned on the edge of the examine bench in a sitting position. All women were asked to perform the Jendrassik's maneuver.

During this maneuver the women are asked to interlock the hands to prevent consciously inhibiting or influencing the response. This is a method that has also been used by other authors (3, 4). This maneuver has an effect on amplitude, but not on the latency (4). If the patellar reflex was not measurable in both legs, even with the Jendrassik's maneuver, then women were excluded from analysis. For statistical analysis the highest amplitude and the corresponding shortest latency was used.

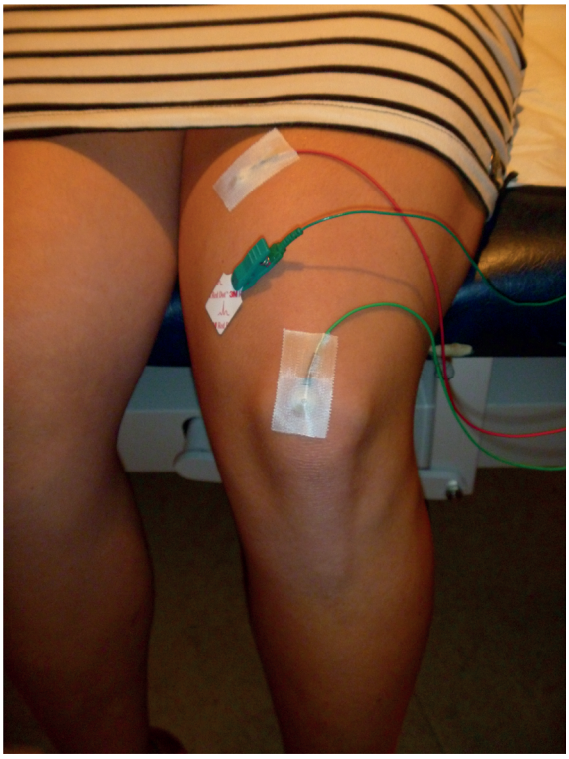

Figure 2. Placement of the surface electrodes.

All data were analyzed using the statistical software package SPSS 20.0 (SPSS, Chicago, IL, USA). To test for normality data were analyzed with the Kolmogorov-Smirnov test. If data were normally distributed *p*-values were obtained with an oneway ANOVA. When data were not normally distributed *p*-values were obtained with a Kruskal-Wallis test. Multivariable linear regression analysis was used in data of pregnant and postpartum women to test the association between preeclampsia, latency and amplitude. For right-skewed continuous data a log transformation was performed before linear regression.

Results

During the study period 241 women were consecutively recruited from our in- and outpatient clinic. The patellar reflex was recorded in 208 pregnant women (161 normotensive pregnant and 47 preeclamptic women) and 33 non-pregnant women. In 12 healthy pregnant women, four preeclamptic women and five former preeclamptic postpartum women the reflex was recorded, but was not measurable and therefore could not be used in the analysis.

The demographic characteristics of the data are presented in Table 1 and Table 2. Table 1 shows that the characteristics between the non-pregnant and normotensive gestational age groups differed significantly for age, systolic and diastolic blood pressure. When we compared the demographics between normotensive and preeclamptic women, there were differences seen in weight, systolic and diastolic blood pressure (Table 2). In this group use of antihypertensive medication also showed a difference between the groups. When we compared the use of medication between mild and severe preeclamptic women no difference was seen (p=0.277). The postpartum data showed higher systolic and diastolic blood pressures and more medication use in formerly preeclamptic women. Between the mild and the severe formerly preeclamptic women there were no differences in medication use (p=1.000) or other demographic characteristics (age; p=0.278, length; p=0.888, weight; p=0.061, BMI; p=0.118, systolic blood pressure in pregnancy; p=0.072, diastolic blood pressure in pregnancy; p=0.179, systolic blood pressure postpartum; p=0.245, diastolic blood pressure postpartum; p=0.301). There were no significant differences in latency and amplitude of the CMAP in normotensive pregnancies between the non-pregnant, pregnant and postpartum groups (Table 1). Table 2 shows that there was a significant increase in mean latency between the three pregnant groups of women concomitant with the severity of the hypertensive disorder (p=0.045). The median amplitude decreased simultaneously but not significantly. These differences disappeared in the postpartum period (Table 2).

Factors associated with latency and amplitude were examined in multivariable linear regression analysis to control for potential confounders (Table 3). Use of antihypertensive medication appeared only to be a confounder for amplitude in pregnancy. Latency continues to be significantly different between normotensive and severe preeclamptic pregnant women, even when data are adjusted for maternal age and height. Latency appeared not to be significantly different in the postpartum group between severe preeclamptic compared to normotensive women. After adjusting for age and height significance was borderline (p=0.05). In pregnant and postpartum women multivariable analysis of amplitude did not show differences between normotensive and preeclamptic women for both crude and adjusted data. The variables height and BMI are highly correlated. We choose height as a variable in the multivariable analysis, not the derived variable BMI. Effect modification of maternal age, height and antihypertensive medication in relation to preeclampsia was explored, but not found.

Table 1. Data of normotensive women (n=218)

	Non-pregnant (n=33)		Normotensive 12-14 weeks pregnant (n=40)		Normotensive 26-28 weeks pregnant (n=38)		Normotensive 32-34 weeks pregnant (n=34)		Normotensive 36-40 weeks pregnant (n=49)		Normotensive 6-8 weeks postpartum (n=24)		*p*-value
	n[a]		n[a]		n[a]		n[a]		n[a]		n[a]		
Demographic characteristics													
Age (years)[b]	33	26.0 (19.0 - 40.0)	35	34.0 (23.0 - 47.0)	33	33.0 (25.0 - 42.0)	29	34.0 (19.0 - 41.0)	44	32.0 (20.0 - 42.0)	20	34.0 (25.0 - 42.0)	0.027[d]
Length (cm) [c]	33	170.7 ± 6.2	35	166.5 ± 8.2	33	168.9 ± 8.0	29	168.1 ± 8.9	44	167.5 ± 8.7	20	171.5 ± 7.6	0.308[e]
Weight (kg)[b]	32	67.0 (52.0 - 98.0)	35	65.0 (50.0 - 88.0)	33	67.0 (50.0 - 117.0)	29	64.0 (52.0 - 108.0)	44	68.5 (46.0 - 108.0)	20	72.0 (50.0 - 92.0	0.668[d]
BMI[b]	32	22.5 (18.4 - 36.0)	35	23.5 (18.7 - 33.1)	33	23.5 (18.0 - 39.5)	29	22.6 (17.3 - 37.2)	44	23.9 (16.9 - 40.7)	20	23.2 (18.8 - 31.9)	0.698[d]
Systolic blood pressure (mm Hg)[b]	32	120 (90 - 130)	35	110 (90 - 145)	33	110 (100 - 136)	29	110 (90 - 130)	44	120 (100 - 142)	20	110 (95 - 135)	0.001[d]
Diastolic blood pressure (mm Hg)[b]	32	70 (50 - 80)	35	60 (50 - 90)	33	65 (50 - 88)	29	70 (50 - 90)	44	70 (55 - 85)	20	70 (50 - 85)	0.004[d]
Latency and amplitude													
Latency (ms) [c,f]	33	22.13 ± 2.93	36	21.25 ± 1.97	36	21.29 ± 2.66	33	21.22 ± 2.47	44	21.38 ± 2.17	24	21.83 ± 2.27	0.574[e]
Amplitude (mV) [b,f]	33	2.50 (0.40 - 6.20)	36	1.70 (0.50 - 5.00)	36	2.20 (0.20 - 6.90)	33	2.70 (0.30 - 6.20)	44	2.10 (0.20 - 6.60)	24	1.60 (0.30 - 4.50)	0.336[d]

[a] Number of women from whom the variable was obtained
[b] Median (range)
[c] Mean ± SD
[d] *P*-values obtained with a Kruskal-Wallis test
[e] *P*-values obtained with a oneway ANOVA test
[f] Latency corresponding with the maximal amplitude
Abbreviations: n, number; cm, centimeters; kg, kilograms; BMI, body mass index; ms, milliseconds; mV, milliVolt

Table 2. Data of pregnant (n=208) and postpartum women (n=71)

	Normotensive		Mild pre-eclampsia		Severe pre-eclampsia		*p*-value
	n[a]		n[a]		n[a]		
Demographic characteristics							
Pregnant women	**161**		**14**		**33**		
Age (years)[b]	160	33 (19 - 47)	14	33.0 (26.0 - 41.0)	33	29.0 (18.0 – 42.0)	0.270[e]
Length (cm) [c]	151	167.5 ± 8.3	14	169.2 ± 6.2	33	168.9 ± 7.0	0.532[f]
Weight (kg)[b]	147	67 (46 - 118)	14	78.0 (55.0 – 130.0)	32	69.5 (50.0 – 108.0)	0.034[e]
BMI[b]	146	23.5 (16.9 - 40.7)	14	27.2 (17.4 – 46.1)	32	23.3 (18.4 – 38.3)	0.102[e]
Systolic blood pressure (mm Hg)[b]	156	110 (90 - 145)	12	133 (110 – 150)	33	140 (105 – 164)	0.000[e]
Diastolic blood pressure (mm Hg)[b]	156	65 (50 - 90)	12	90 (70 – 95)	33	90 (79 – 110)	0.000[e]
Use of antihypertensive medication [d]	161	0 (0.0%)	14	9 (64.3%)	31	25 (80.6%)	0.000[g]
Postpartum women	**24**		**14**		**33**		
Age (years)[b]	24	33.5 (25 - 42)	14	33.0 (26 - 41)	33	29 (18 - 42)	0.331[e]
Length (cm) [c]	22	170.4 ± 8.0	14	169.2 ± 6.2	33	168.9 ± 7.0	0.744[f]
Weight (kg)[b]	22	71 (50 - 92)	14	78 (55 - 130)	32	69.5 (50 - 108)	0.132[e]
BMI[b]	22	23.2 (18.8 - 31.9)	14	27.2 (17.4 - 46.1)	32	23.3 (18.4 - 38.3)	0.232[e]
Systolic blood pressure (mm Hg)[b]	20	110 (95 - 135)	10	130 (100 - 145)	29	125 (100 - 190)	0.009[e]
Diastolic blood pressure (mm Hg)[b]	20	70 (50 - 85)	10	85 (65 - 100)	29	80 (50 - 110)	0.010[e]
Use of antihypertensive medication [d]	24	0 (0.0%)	14	5 (35.7%)	32	11 (34.4%)	0.004[g]
Latency and amplitude							
Pregnant women	**161**		**14**		**33**		
Latency (ms) [c,h]	149	21.29 ± 2.30	12	21.92 ± 1.76	27	22.42 ± 2.08	0.045[f,i]
Amplitude (mV) [b,h]	149	2.10 (0.20 - 6.90)	12	1.80 (0.50 - 7.30)	27	1.60 (0.40 - 9.70)	0.172[e]
Postpartum women	**24**		**14**		**33**		
Latency (ms) [c,h]	24	21.83 ± 2.27	11	21.67 ± 1.65	17	22.23 ± 1.12	0.807[f]
Amplitude (mV) [b,h]	24	1.60 (0.30 - 4.50)	11	1.20 (0.40 - 6.30)	17	1.10 (0.40 - 4.50)	0.548[e]

[a] Number of women from whom the variable was obtained

[b] Median (range)

[c] Mean ± SD

[d] Number (percentage)

[e] *P*-values obtained with a Kruskal-Wallis test

[f] *P*-values obtained with a one-way ANOVA test

[g] *P*-values obtained with a chi-squared test

[h] Latency corresponding with the maximal amplitude

[i] Significant difference between normotensive pregnant and severely preeclamptic women

Abbreviations: n, number; cm, centimeters; kg, kilograms; BMI, body mass index; ms, milliseconds; mV, milliVolt

Table 3. Multivariable analysis of pregnant (n=208) and postpartum women (n=71)

Outcome measure	Crude			Adjusted		
	B	95% CI	*P*-value	B	95% CI	*p*-value
Pregnant women						
Latency (ms)[a]						
All PE vs. normotensive	.976	.182 - 1.770	0.016	.811	.140 - 1.483	0.018
Mild PE vs. normotensive	.626	-.700 - 1.953	0.353	.175	-.923 - 1.274	0.753
Severe PE vs. normotensive	1.132	.207 - 2.056	0.017	1.102	.323 - 1.880	0.006
Amplitude (mV)[b,c]						
All PE vs. normotensive	-.088	-.205 - .029	0.140	-.029	-.164 - .107	0.678
Mild PE vs. normotensive	-.020	-.218 - .178	0.839	.025	-.177 - .226	0.810
Severe PE vs. normotensive	-.117	-.253 - .019	0.090	-.057	-.215 - .100	0.474
Postpartum women						
Latency (ms)[a]						
All PE vs. normotensive	.375	-.985 - 1.735	0.583	.865	-.375 - 2.106	0.167
Mild PE vs. normotensive	.037	-1.764 - 1.838	0.967	.134	-1.413 - 1.681	0.862
Severe PE vs. normotensive	.593	-.971 - 2.158	0.450	1.418	.001 - 2.835	0.050
Amplitude (mV) [b,c]						
All PE vs. normotensive	-.119	-.294 - .056	0.178	-.125	-.327 - .077	0.220
Mild PE vs. normotensive	-.077	-.316 - .162	0.520	-.075	-.330 - .181	0.560
Severe PE vs. normotensive	-.141	-.336 - .054	0.153	-.156	-.380 - .068	0.170

[a] Adjusted for age (years) and height (cm)

[b] Adjusted for age (years), height (cm) and use of antihypertensive medication

[c] Log transformed data used

Abbreviations: ms, milliseconds; mV, milliVolt; B, regression coefficient; CI, confidence interval; PE, preeclampsia

Discussion

In this study, we present data of the patellar reflex during normotensive pregnancies and pregnancies with preeclampsia measured with SEMG. Quantifying the outcome of the reflex eliminates the personal interpretation, and standardizes the assessment. Our results show that there are no significant differences in latency and amplitude of the patellar SEMG during the course of normotensive pregnancies. We were not able to show differences during any period in normotensive pregnancies as compared to non-pregnant and postpartum pregnancies. Latency, not amplitude, appeared to be significantly different between normotensive and severe preeclamptic women. Age,

height and use of antihypertensive medication appeared to be confounding factors. Latency continued to be significant even after correcting for these confounding factors.

One article, on normative data of the patellar reflex evoked CMAP in the vastus medialis muscle, contains data of males and females (3). Only five studies were found on the patellar reflex during pregnancies with preeclampsia or eclampsia (9-13). However, none of these studies used SEMG to quantify the reflex response. Several studies have shown that nerve conduction speed decreases with age and therefore has an influence on latency (5, 6, 14-16). As shown by many authors, latency is also strongly correlated with the height of the individual (4-6, 15, 16). Latency lengthens with increasing height. Surprisingly, none of these studies corrected their data for age or height of the individuals. Because they did not categorize their data according to sex, age and height we could not compare our findings with these data. In Table 1 we show significant differences in age and systolic and diastolic blood pressure between the different normotensive study groups. In our study all the participants were of reproductive age, ranging from 20 to 40 years. Although our non-pregnant group was significantly younger than our pregnant groups, this difference was not large enough to lead to differences in latency or amplitude of the patellar SEMG.

Most studies on the patellar reflexes during pregnancies with preeclampsia suggest an increased response as a clinical important hallmark. However, all studies lacked quantitative data. The present study is the first to describe these quantitative data, but we failed to show an increased response in preeclamptic women. A possible explanation is that the blood pressure in all women in our study had been reduced by antihypertensive drugs before the measurements were performed. Also, none of our preeclamptic patients developed eclampsia or other serious cerebral complications. Another possible disadvantage of this study is the wide range of the measurements, which makes it more difficult to show statistically different results. This range is larger during pregnancy and especially during pregnancies with severe preeclampsia.

In contrast to what was expected, the latency and, although not significant, amplitude, showed a slower and less pronounced response of the CMAP, also after correction for age, height and use of medication. We speculate that the formation of edema, both locally and/or in the myelin sheaths may lead to slowing of the nerve conduction. The results of the multivariable analysis rule out that antihypertensive medication or magnesium sulphate influence the resting potential of the axons. In the severe preeclamptic group of women only 3/29 women received magnesium sulphate during the measurements. The individual data of these three women were not statistically different (data not shown).

In conclusion, the patellar reflex can be objectively assessed using SEMG. Gestational age has no effect on the patellar reflex during the course of normotensive pregnancy.

Assessment of deep tendon reflexes with SEMG in stabilized patients with preeclampsia is probably not suitable for clinical bedside assessment and follow-up of preeclamptic patients. Future studies regarding the patellar reflex in preeclampsia should address the untreated preeclamptic patient.

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Literature

1. Stam J, van Crevel H. Reliability of the clinical and electromyographic examination of tendon reflexes. Journal of neurology. 1990;237:427-31.
2. Sharma KR, Saadia D, Facca AG, Resnick S, Ayyar DR. Diagnostic role of deep tendon reflex latency measurement in small-fiber neuropathy. J Peripher Nerv Syst. 2007;12:223-31.
3. Alisauskiene M, Magistris MR, Vaiciene N, Truffert A. Electrophysiological evaluation of motor pathways to proximal lower limb muscles: a combined method and reference values. Clin Neurophysiol. 2007;118:513-24.
4. Frijns CJ, Laman DM, van Duijn MA, van Duijn H. Normal values of patellar and ankle tendon reflex latencies. Clinical neurology and neurosurgery. 1997;99:31-6.
5. Kuruoglu R, Oh SJ. Quantitation of tendon reflexes in normal volunteers. Electromyography and clinical neurophysiology. 1993;33:347-51.
6. Pereon Y, Nguyen The Tich S, Fournier E, Genet R, Guiheneuc P. Electrophysiological recording of deep tendon reflexes: normative data in children and in adults. Clin Neurophysiol. 2004;34:131-9.
7. Bulletins--Obstetrics ACoP. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99:159-67.
8. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631-44.
9. Chao A. The patellar reflex in preeclamptic women with subtherapeutic and therapeutic serum magnesium levels. The Journal of reproductive medicine. 1990;35:678-81.
10. Lawson J. Eclampsia. Clinics in obstetrics and gynaecology. 1982;9:711-21.
11. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clinical pharmacokinetics. 2000;38:305-14.
12. Oney T, Weitzel H. New aspects of anticonvulsive therapy in severe pre-eclampsia and eclampsia. Geburtshilfe und Frauenheilkunde. 1989;49:906-14.
13. Thurnau GR, Dyer A, Depp OR, 3rd, Martin AO. The development of a profile scoring system for early identification and severity assessment of pregnancy-induced hypertension. American journal of obstetrics and gynecology. 1983;146:406-16.
14. Chung SG, Van Rey EM, Bai Z, Rogers MW, Roth EJ, Zhang LQ. Aging-related neuromuscular changes characterized by tendon reflex system properties. Archives of Physical Medicine and Rehabilitation. 2005;86:318-27.
15. Stam J, van Crevel H. Measurement of tendon reflexes by surface electromyography in normal subjects. Journal of neurology. 1989;236:231-7.
16. Struys MA, Jonkman EJ, Strijers RL. Measurement of patellar and ankle tendon reflexes in normal subjects. Electromyography and clinical neurophysiology. 1997;37:13-8.

CHAPTER 7

Impaired maternal cognitive functioning after pregnancies complicated by severe preeclampsia: a pilot case-control study

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Abstract

Background

Preeclampsia is the most significant cause of neurological symptoms in pregnancy. Neurological symptoms may persist even after pregnancy. Somatic symptoms of preeclampsia, such as hypertension and proteinuria, generally disappear after delivery. However, formerly preeclamptic women more often complain of cognitive disturbances compared to women after uncomplicated pregnancies.

Methods

Three to eight months postpartum, a neuropsychological test battery was performed in 10 former severely preeclamptic women (according to the guidelines of the American College Obstetricians and Gynecologists) and 10 women after uncomplicated normotensive pregnancies. The control group was matched for age, educational level and mode of anesthesia. All women delivered by cesarean section either under general or regional anesthesia. Tests were performed for premorbid intelligence, short- and long-term memory, attention, concentration, executive functions, visual and spatial abilities. Anxiety and depression levels were measured.

Results

The formerly preeclamptic women had significantly lower scores on most indices of the auditory-verbal memory test. Formerly preeclamptic patients learned considerably fewer words than controls and recalled less after interference. Both case and control group did not differ in age, parity or level of education. There were no differences in the level of intellectual functioning and language tests, such as naming and word fluency. No persistent differences were observed in tests for attention/concentration and executive functioning. There were no significant differences on depression and anxiety scales.

Conclusions

Maternal memory seems to be impaired after pregnancies complicated by severe preeclampsia. This effect cannot be attributed to depression and/or anxiety or method of anesthesia.

Introduction

Preeclampsia is a multi-organ disease of unknown cause that is unique to human pregnancy. It affects 1-7% of all pregnancies. During the period of clinical disease, laboratory tests and imaging techniques are used to assess the condition of the feto- placental unit and maternal hemostasis, as well as liver, kidney and lung function. Additionally, preeclampsia affects the maternal brain. Cerebral complications, such as eclamptic seizures and hemorrhage, are the main cause of preeclampsia-related maternal deaths (1). In imaging studies, eclamptic seizures have been shown to cause permanent cerebral damage (2). (Pre-)eclampsia can result in cognitive impairments, such as perceived loss of memory and concentration (3). Although these cognitive complaints are usually relatively mild, they can persist, and sometimes interfere with daily functioning and work. Unfortunately, little is known about the long-term effects of pre- eclampsia on cognitive functioning. To our knowledge, there are no studies published that have systematically investigated cognitive functioning with standardized neuropsychological tests postpartum in previously severely preeclamptic patients. Therefore, the objective of this study is to compare important cognitive functions (language, memory, abstraction, attention, executive functioning and visuoconstruction) 3-7 months after delivery in former severely preeclamptic women and women after an uncomplicated pregnancy.

Material and Methods

A case-control study comparing cognitive functions 3-7 months after delivery in 10 former severely pre- eclamptic patients (case group) and 10 women who had normotensive pregnancies (control group), was performed. After obtaining informed consent, patients were included in this study from April 2004 to April 2006. The main inclusion criterion for the cases was a pregnancy complicated by severe preeclampsia. Severe preeclampsia was defined according to the guidelines of the American College of Obstetricians and Gynecologists (ACOG; see textbox 1) (4).

Textbox 1. ACOG (4) criteria for severe preeclampsia

Hypertension (systolic blood pressure ≥140 mmHg or diastolic ≥ 90mmHg) and de novo proteinuria (≥ 300 mg per 24 h) and the presence of one or more of the following criteria:

- systolic blood pressure ≥160 mmHg or diastolic ≥110 mmHg on 2 occasions, at least 6 h apart while bed rest
- proteinuria of 5 g or more in a 24-h urine specimen
- oliguria of ≥ 500 ml in 24 h
- persistent headache or cerebral or visual disturbances
- epigastric or right upper-quadrant pain
- increased serum creatinine level
- impaired liver function
- thrombocytopenia
- fetal growth restriction

The control group was matched for age, educational level, mode of delivery, and method of anesthesia. Patients were excluded when a reliable assessment of cognitive functions could not be made due to insufficient command of the Dutch language, severe sensory handicaps (e.g. deafness or blindness) or severe psychiatric symptoms. Women who had experienced perinatal death were also excluded from the study. None of the pregnancies was complicated by eclampsia, pulmonary edema or liver rupture. The case group was asked to enroll directly postpartum and the control group 6 weeks postpartum while visiting the out-patient clinic. All of the women included, both cases and controls, were delivered by cesarean section under general or regional anesthesia. Eight women in both groups were delivered under general anesthesia. Five of the women in the control group underwent a scheduled cesarean section because of breech position (n =3), vasa previa (n =1) and cephalopelvic dysproportion (n =1). The other 5 women underwent an emergency cesarean section because of poor progression of labour (n =1), signs of fetal distress (n =3) and cephalopelvic dysproportion (n =1).

The neuropsychological test battery was per-formed 3-7 months postpartum when the physical complications had largely disappeared and laboratory tests in the patients of the case group had normalized. The control group was tested during the same postpartum period.

As the extent and distribution of the cognitive complaints is unclear, we composed a test battery that covers multiple cognitive domains, e.g. premorbid intelligence, short- and long-term memory, abstraction, attention, executive functioning, visual and spatial abilities. As depression and anxiety are known as the main possible confounders

for performance on memory and attention tasks, specific questionnaires were given to establish their contribution on the neuropsychological test results.

The Nederlandse Leestest voor Volwassenen (NLV), the Dutch version of the National Adult Reading Test, is a reading test of 50 words with irregular pronunciation that provides an estimation of premorbid level of functioning (5). Auditory verbal memory was examined with the Dutch version of the Rey auditory verbal learning test (6). A list of 15 words is presented orally with 5 learning trials. Delayed free recall and recognition followed after 15 min. The Digit Span forward and backward, a subtest of the Wechsler Adult Intelligence Scale (WAIS), was used to assess the span of immediate verbal recall, but also served as a measure of attentional capacity and working memory (7,8). Patients have to repeat a sequence of digits of increasing length in both forward and reverse order. The Trail Making Test, and the Stroop Color Word test were also used to measure attention (9,10). In the Trail Making Test, patients have to connect either numbers (psychomotor speed), or numbers and letters alternately (concept-shifting). The Stroop Color Word Test consists of 3 cards. On the first card, 100 color names (red, blue, green, yellow) should be read aloud, on the second card patients have to name the color of 100 printed names, all printed in different colors. The color name does not correspond with the color of the ink, and patients have to name the color of the ink, and not read the word. Verbal fluency was measured by the number of words mentioned in 1 min. Semantic fluency was determined by the number of animals and professions, phonological fluency by the number of words starting with a D, A, or T (7). Scores on verbal fluency, Stroop Color Word Test part III and Trail Making Test B served as an indication for the level of executive functioning. Visuoconstructive functioning was measured with Block Design, in which the patients have to reproduce a printed block design with three-dimensional blocks (WAIS) (8) and draw a clock (11). Levels of anxiety and depression were measured by the State-Trait Anxiety Inventory (STAI) and Center for Epidemiological Studies Depression Scale (CES-D) (12,13). Education was categorized according to the system of Verhage (14), which consists of 7 levels of increasing level of education, from 1 (only primary school) to 7 (university).

Due to the small sample size, non-parametrical statistical analysis using the Wilcoxon rank test was performed using Statistical Package for the Social Sciences (SPSS) 15.0 for Windows. A p-value of 0.05 was considered significant.

Results

There was no statistical difference between groups in age, parity, level of education, and interval between delivery and neuropsychological testing (Table 1). The gestational age differed between the 2 groups.

Table 1. Demographic characteristics

	Cases (N=10)		Controls (N=10)		P-value
	median	range	median	range	
Age (years)	34.4	29.2-37.4	33.8	29.4-37.2	0.88
Parity (number)	1.4	0-3	1.6	0-3	0.53
Level of education ˚	5.5	4-7	6	4-7	0.56
Gestational age at delivery (weeks)	30	27-33	38.5	27-41	0.009*
Interval delivery - neuropsychological-testing (months)	3.5	3-7	3	3-7	0.75

Both groups are compared with the Wilcoxon rank test. *P < 0.05 is considered significant

˚ Education was categorized according to the system of Verhage.

The case group had significantly lower scores on most indices of the auditory-verbal memory test (Table 2). Former preeclamptic patients learned considerably fewer words than controls (50 versus 62), and recalled less after interference (10 versus 14). The passive recognition condition showed a ceiling effect in both the case and control group.

Table 2. Neuropsychological test results

		Cases (N=10)		Controls (N=10)		P-value
		Median	Range	Median	Range	
Intelligence quotient˚		104	94-115	103	97-111	0.76
Language	Boston Naming Test (max. 60)	52	47-57	51.5	35-55	0.55
	Semantic Fluency -animals (no. per 60 sec.)	23.5	19-31	24.5	17-33	0.55
	-professions (no. per 60 sec.)	16	8-22	18	13-21	0.13
	Phonological fluency (no. per 60 sec.)	32.5	20-46	38	23-53	0.26
Memory	Learning (max. 75)	49	43-57	63.5	53-70	0.005*
	Recall (max. 15)	10	7-13	14.5	11-15	0.008*
	Recognition (max. 30)	30	29-30	30	30-30	0.08
Abstraction	Similarities (WAIS) (max. 33)	23	16-29	25.5	19-32	0.06
Attention & executive functioning	Letter-number sequencing (WAIS) (max. 21)	10	9-13	11	8-14	0.61
	Digit span (WAIS) (max. 30)	16.5	12-24	16.5	13-19	0.41
	Trail Making Test A (time in sec.)	23.5	15-37	35.5	20-52	0.03*
	Trail Making Test B (time in sec.)	49.5	36-75	62.5	46-100	0.20
	Stroop, part I (time in sec.)	43	35-69	46	35-108	0.29
	Stroop, part II (time in sec.)	56	44-75	59.5	49-89	0.39
	Stroop, part III (time in sec.)	81.5	62-115	90	68-122	0.58
Visuoconstruction	Block design (WAIS) (max. 68)	39	12-65	38.5	9-63	0.77
	Clock drawing (max. 14)	12	11-13	12	10-14	0.38
Personality	Depression (CES-D)	7.5	0-32	8	0-21	0.67
	Anxiety (STAI-2)	39	20-56	31	20-44	0.21

Groups are compared with the Wilcoxon rank test.. * P < 0.05 is considered significant.

˚Measured by NLV.

There were no differences in level of intellectual functioning, regarding the scores on the NLV. Language tests, i.e. naming and word fluency, showed comparable scores for both groups. In addition, no persistent differences were observed in attention and concentration tests, except for a significant difference in favor of the case group for Trail Making Test A. Results on tests for executive functioning were equal in both groups. Although the cases had somewhat higher scores on the CES-D (depression) and the STAI (level of anxiety), the differences did not reach significance (CES-D: $p = 0.67$, STAI: $p = 0.21$).

Discussion

To date, research of preeclampsia has focused on the etiology, pathogenesis and somatic consequences of the disease. However, as somatic symptoms merely disappear after delivery, many women continue to complain of cognitive disturbances.

This pilot study shows that memory is impaired in women who suffered from severe preeclampsia. The lower scores on the memory measures are consistent over the indices. This impairment probably results from the presence of lesions in the brain of preeclamptic women due to cerebral ischemia and edema in the clinical phase of the disease (15). It is not unlikely that (part of) the memory deficit may be permanent since radiological studies have shown signs of permanent damage in the white matter of the brains of patients that suffered eclamptic fits (1). Studies on localization of brain damage as a cause of organic amnesia suggest the loss of volume in key brain structures, such as hippocampus and thalamus (16). However, it is still not known whether such lesions are also present in the brains of severe preeclamptic women. Functional imaging studies may provide more insight in localization of this specific type of brain damage.

An alternative explanation for the memory disturbances could be the influence of psychological factors in patients that experienced preeclampsia. These women experience an emotional burden of the care for their premature child and their own serious illness, which may result in stress and mood changes, such as depression and anxiety. However, as in our study scores on depression and anxiety questionnaires were similar in both groups, this explanation seems unlikely (Table 2).

The clinical impression of diminished attention and concentration could not be confirmed in the formerly preeclamptic patients. In these domains, there were no significant differences between the 2 groups, but surprisingly there was a trend towards better scores in the case group. One part of the test, the Trail Making Test A, even showed a significantly better score by the patient group. As this was an isolated finding in the whole domain of attention tests, this is presumably a random result.

Recent studies on cognitive functioning during uncomplicated pregnancy have shown that compared to non-pregnant women, performance on memory tests is decreased from early pregnancy to 32 weeks' postpartum, whereas psychomotor speed and executive functioning remains unchanged (17,18).

Possible explanations for this pregnancy-related memory loss are based on the large change in several hormonal systems during pregnancy.

In our present study, an even larger memory deficit was observed in patients after pregnancies complicated by severe preeclampsia.

In another recent study, cognitive functioning was studied before and shortly after delivery in pre- eclamptic patients and healthy controls (19). In this study, all pregnant patients had lower scores on memory measures compared to non-pregnant controls. On the other hand, postpartum no statistical differences were found between the patient group and the control group in measures for memory and attention, but there was no differentiation made between mild and severe preeclampsia.

Although inherent to a pilot study, an obvious restriction of the present study is the limited sample size. It is underpowered to detect small differences between groups. It could, however, be calculated that our study had sufficient power (80%) to detect differences in scores on the learning memory test of ≥6 and the recall memory test of ≥3, respectively.

Furthermore, we dealt with the restriction of small sample size by strict matching for relevant factors. Since the differences in memory measures are significant and consistent over multiple indices, even in these relatively small groups of patients, this finding may be considered as a genuine effect of severe preeclampsia. To resolve the major question of whether the observed memory deficits are temporary or permanent, al longer follow-up study is needed. The long span of 3-7 months between delivery and testing may have been a disadvantage. However, considering the findings of a recent study, which found no changes in cognitive functioning during a follow-up time of 32 weeks' postpartum, it is unlikely that this played a substantial role (18).

Conclusion

The present study shows that severe preeclamptic patients have at least longstanding cognitive function difficulties in especially short- and long-term memory. This may have consequences for their postpartum return to normal life and work. It is not clear whether this memory deficit can be influenced by earlier intervention or another symptomatic treatment of preeclampsia, and can probably be improved by postpartum neuropsychological training programs. The organic damage causing this memory deficit and whether it is permanent or temporary must be elucidated. Severely preeclamptic patients may

thus have at least some longstanding cognitive function difficulties in especially short and long term memory. This may have consequences for their postpartum return to normal life and work. It is not clear whether this memory deficit can be influenced by earlier intervention or symptomatic treatment of preeclampsia or whether post partum neuropsychological training programs can improve it. It has to be eluded what organic damage causes this memory deficit and whether it is permanent or temporary.

Literature

1. Lewis G, Drive J. Why mothers die1997-1999. Fifth report on confidential inquiries into maternal deaths in the United Kingdom 1997-1999. London: RCOG Press; 2001.
2. Zeeman GG, Fleckenstein JL, Twickler DM, Cunningham FG. Cerebral infarction in eclampsia. Am J Obstet Gynecol 2004;190:714-20.
3. Roes EM, Raijmakers MT, Schoonenberg M, Wanner N, Peters WH, Steegers EA. Physical well-being in women with a history of severe preeclampsia. J Matern Neonatal Med 2005;18:39-45.
4. American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia: ACOG practice bulletin. Number 33. Int J Gynecol Obstet 2002;77:67-75.
5. Schmand B, Lindeboon J, van Harskamp F. Dutch adult reading test. Manual. Lisse: Swets & Zeitlinger, 1992.
6 . Saan RJ, Deelman BG. Dutch version of the Rey auditory verbal learning test. Groningen: Department of Neuropsychology, RUG, 1986.
7. Luteijn F, Vanderploeg FAE. Groninger Intelligentie Test Manual.Lisse: Swets & Zeitlinger BV, 1983.
8. Wechsler D, Stone C. Manual for the Wechsler Adult Intelligence Scale. Manual. New York.: The psychological Corporation, 1955.
9. Reitan RM. Validity of the Trail Making Test as an indication of organic brain damage. Percept Mot Skills 1958;8:271-6.
10. Hammes JG. Stroop kleur-woord Test: Dutch manual. Manual. Lisse: Swets & Zeitlinger, 1978.
11. Royall DR, Cordes JA, Polk M. CLOX: an executive clock drawing task. J Neurol Neurosurg Psychiatry 1998;64:588-94.
12. Van der Ploeg HM. Dutch version of the Spielberger State-Trait Anxiety Inventory. Manual. Lisse: Swets & Zeitlinger, 2000.
13. Bouma J, Ranchor AV, Sanderman R, van Sonderen E. CES-D scale. Manual. Groningen: RUG, 1995.
14. Verhage F. Intelligence and age: Research among the Dutch between 7 and 77 years of age. Assen: Van Gorcum, 1964.
15. Schwartz RB, Feske SK, Polak JF, DeGirolami U, Iaia A, Beckner KM et al. Preeclampsia-eclampsia: clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. Radiology 2000;217:271-6.
16 Kopelman MD, Lasserson D, Kingsley D, Bello F, Rush C, Stanhope N et al. Structural MRI volumetric analysis in patients with organic amnesia, 2: correlations with anterograde memory and executive tests in 40 patients. J Neurol Neurosurg Psychiatry 2001;71:23-8.
17 de Groot RH, Hornstra G, Roozendaal N, Jolles J. Memory performance, but not information processing speed, may be reduced during early pregnancy. J Clin Exp Neuropsychol 2003;25:482-8.
18 de Groot RH, Vuurman EF, Hornstra G, Jolles J. Differences in cognitive performance during pregnancy and early motherhood. Psychol Med 2006;36:1023-32.
19 Rana S, Lindheimer M, Hibbard J, Pliskin N. Neuropsychological performance in normal pregnancy and preeclampsia. Am J Obstet Gynecol 2006;195:186-91.

CHAPTER 8

General discussion

Introduction

This thesis describes the results of a single center observational study on neurophysiological manifestations in normotensive and hypertensive pregnancies, the ROtterdam BRAin function study (the ROBRA study). Various neurophysiological measurements were performed both during pregnancy and postpartum.

Preeclampsia is a multi-organ disease of unknown cause that is confined to human pregnancy. Preeclampsia affects 1-7% of all pregnancies (1). Neurologic complications due to hypertensive disease in pregnancy are among the leading causes of maternal morbidity and mortality (2).

In this thesis we used the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP), defining pregnancy induced hypertension (PIH) as de novo hypertension after 20 weeks of gestation and preeclampsia if hypertension is combined with proteinuria (3). The severity of the disease was defined according to the criteria of the American College of Obstetricians and Gynecologists (ACOG) (textbox 1) (4). Stabilization of women with severe preeclampsia was considered to be fulfilled after normalization of hypertension by antihypertensive medication and institution of anticonvulsive prophylaxis (magnesium sulfate). Stabilization of severe preeclamptic patients is of utmost importance to diminish the risks of adverse outcome (1).

Textbox 1. ACOG (4) criteria for severe preeclampsia

Hypertension (systolic blood pressure ≥140 mmHg or diastolic ≥ 90mmHg) and de novo proteinuria (≥ 300 mg per 24 h) and the presence of one or more of the following criteria:

- systolic blood pressure ≥160 mmHg or diastolic ≥110 mmHg on 2 occasions, at least 6 h apart while bed rest
- proteinuria of 5 g or more in a 24-h urine specimen
- oliguria of ≥ 500 ml in 24 h
- persistent headache or cerebral or visual disturbances
- epigastric or right upper-quadrant pain
- increased serum creatinine level
- impaired liver function
- thrombocytopenia
- fetal growth restriction

Preeclampsia may have devastating effects on a women's health and may lead to severe maternal morbidity and even mortality. This is particularly the case when cerebral pathology appears. A definite measure to detect and to follow brain function and possible

damage is still not available. It is, however, of great importance to detect this brain damage in an early phase where it may still be reversible.

Clinical signs and symptoms of cerebral manifestations of the disease are headaches, eclampsia, visual disturbances and cortical blindness. In the periferal nervous system increased tendon reflexes may be observed. Cognitive complaints like memory loss, lack of concentration and problems in returning into social life are reported as long term complications (5). Depression and anxiety can also be present after preeclampsia (6). MRI studies of the brain showed more often white matter lesions after pregnancies complicated by eclampsia than after normotensive pregnancies (7, 8)

The main purpose of our investigations was to develop tools to follow and detect changes in maternal brain function during and after pregnancies complicated by hypertensive disease of pregnancy. We chose to use routine neurophysiological tests in this thesis. Studies were performed with Electroencephalography (EEG) which gives an overview of the brain function with modest spatial but very high temporal resolution, evaluating entire brain function, Visual Evoked Potentials (VEP) evaluating the visual cortex and Transcranial Doppler (TCD) evaluating cerebral hemodynamics. To measure effects on the periferal nervous system we used Electromyography (EMG) measurements of the patellar reflex.

To study the long term sequelae we repeated the above mentioned neurophysiological tests, and we also performed neuropsychological tests and used questionnaires concerning Health related Quality of Life (HRQoL).

Limitations of the study

We live in a well-organized country with easy access to hospitals and hospital care. This well-organized care resulted in a study population, which, although by definition were having severe preeclampsia, did not suffer from severe complications. For example, none of the patients in our study population developed an eclamptic seizure. In our Dutch health care system people will often have access to care and get treatment before a disease will lead to (extreme) complications. This may have equalized the possible differences in the results between our different study groups.

The neurophysiological tests used in this study are not very practical in daily clinical practice. For EEG and VEP examinations, respectively twenty-three and five surface electrodes are attached to the skull. To attach and to remove these electrodes is time consuming. The whole procedure, including the measurements, lasts one to two hours. During the examination, the patient needs to be at rest and the room needs to be quiet since noise and other disturbances interfere with the results. For hospitalized pregnant women feeling ill, it may therefore be inconvenient to undergo these neurophysiologi-

cal tests. After the examinations, they meet additional limitations when being almost unable to shower to wash the waxes out of their hair, especially when they have intravenous and/or arterial lines. Some of the women decided to resign further study participation for these very practical reasons.

During the time of our studies we had three obstetrical intensive care beds located in one room on our obstetric critical care unit, which was creating a noisy atmosphere. This clearly interfered with the measurements and frequently the duration of the measurements had to be extended to obtain results with good quality. For future work, we like to use an easier technique with a smaller amount of surface electrodes attached, although fewer electrodes will generate less information.

Finally, the inclusion speed in our study was relatively slow due to:

- Restrictions in the availability of an EEG technician in the evenings, nights and weekends;
- Many patients did not want to be included in the study when they heard what the time investment would be.

Electroencephalography

EEG is a technique to measure cortical electrical brain activity. EEG registrations can be used to detect epileptic activity, to detect abnormal activity in sleep disorders or to detect dysfunctional brain areas after cerebrovascular incidents. EEG is the most important diagnostic tool in evaluating patients with possible epilepsy. It can support the diagnosis of epilepsy but it can also assist in classifying underlying epileptic syndromes. Ultimately, EEG is used to detect whether there still is brain activity in comatose patients as part of an organ donor procedure.

In order to make the best clinical use of the EEG, the clinician must understand its strengths and limitations.

Limitations of the EEG are:

- EEG patterns are not specific for just one (neurologic) diagnosis;
- A relatively short EEG recording can miss paroxysmal EEG changes;
- EEG may show an abnormal pattern in a healthy person without any disease symptoms.

As obstetricians we are interested in the diagnostic use of the EEG during (hypertensive) pregnancies. It is common knowledge that reference values for diagnostic tests in pregnancy may be altered due to adaptations of the pregnant body to be able to manage the needs of the pregnancy. The brain of healthy women also seems to adapt

to pregnancy. Important changes occur at the endothelium and blood-brain barrier, the structure and function of the cerebral arteries and arterioles, and cerebral blood flow autoregulation (9). Especially cerebral autoregulation remains stable over a broader range of the blood pressure in normotensive pregnancies (10). Whether the cerebral circulation becomes involved in the disease process of preeclampsia seems to depend on the level of adaptation of the cerebral circulation to pregnancy. In women in whom the cardiovascular system including the cerebrovascular circulation is not adapting properly during pregnancy, this system may deregulate, resulting in preeclampsia/eclampsia.

Preeclampsia has an impact on all internal organs, also on the brain. After giving birth the changes in these organs normally resolve, but some women will continue to have residual signs and symptoms. EEG is a method that can detect (hypoxic) changes in the brain when they are still reversible. We investigated whether we could detect these kinds of changes in the brain of women suffering from preeclampsia. In our observational study we have found lower alpha peak frequencies (chapter 3) in women with severe preeclampsia than in the other study groups. A decrease in APF is related to decreased performance on memory tasks (11). However, in our study during the postpartum period the alpha peak frequency of the women with and without hypertensive disease did not differ any more.

Clinical symptoms of preeclampsia typically involve visual symptoms. This may be explained by dysfunction of the occipital brain areas. A focal impairment in cerebral autoregulation may be the cause of vasodilation and fluid extravasation leading to edema (12). We expected to detect EEG abnormalities to be localized in the posterior areas of the brain, since there is a lesser degree of adrenergic innervation supporting circulatory autoregulation mechanisms possibly leading to more edema. Also, blood pressure, total vascular resistance, electrolytes, osmolality and vasoactive peptides might have influence on excitability of neuronal tissue. The latter effects seem more overwhelming as our EEG study showed that women with severe preeclampsia experience a more diffuse encephalopathy, with slow wave activities, focal sharp waves and epileptiform activity.

Unfortunately, because of logistic and ethical reasons, we were not able to perform EEG's before or during the start of magnesium sulphate administration. Since this medication is always initiated in acute situations, it was not possible to have a neurophysiological technician timely available before and during the first hour of admission of magnesium sulphate; in most cases simultaneously antihypertensive therapy had to be started too. Besides of this, patients had to have some time to decide whether they would be willing to participate in this study. Sibai studied EEG's in women with severe preeclampsia already in 1984 and showed that EEG abnormalities persisted during administration of magnesium sulphate (13).

These findings underline the necessity to seriously consider terminating pregnancy in preeclamptic women who develop this diffuse cerebral involvement in order to protect them from developing possible permanent neurological damage.

Visual Evoked Potential

Our study on VEP showed in normotensive pregnant women neurophysiological adaptation to pregnancy of the visual cortex, an adaptation that seemed to be absent in women with hypertensive disorders of pregnancy (chapter 4). Studies have previously shown that pregnancy is a state with higher neuronal network excitability and a lower seizure threshold (9, 14). However, other neurophysiological adaptations such as those occurring in the visual cortex, are largely unknown.

Our population size was unfortunately not large enough to demonstrate associations between VEP latencies and amplitudes and clinical visual symptoms. Visual symptoms are defined as flashes, scotoma, blurry vision and cortical blindness. As the function of the visual cortex is influenced by preeclampsia, VEP is probably a promising method to measure brain involvement in preeclampsia. In our study we also performed electroretinography (ERG), a method to assess the functioning of the retina itself. In all study participants ERG's were within normal limits. This does not mean that the bloodflow in the retina was not influenced by hypertension, but it appears not to result in retinal dysfunction as can be assessed with VEP. Doppler studies of the retinal artery during preeclampsia have shown retinal vasospasms associated with visual disturbances (15-18). It would be interesting to perform a study combining VEP with Doppler measurements of the retinal artery to test differences between hypertensive patients with and without visual symptoms.

Transcranial Doppler

In our study on cerebral perfusion pressure we found that cerebral perfusion pressure is elevated in patients with preeclampsia despite blood pressure normalization treated with antihypertensive medication (chapter 5). We also found a strong correlation between systemic blood pressure and cerebral perfusion pressure in women suffering from preeclampsia, suggesting that there is at least a partial loss of cerebral autoregulation. This finding confirms the relationship between increasing systolic blood pressure and the risk to develop eclampsia, which was clinically demonstrated before (19).

Therefore, we conclude, that it is of upmost importance to regulate blood pressure within strict limits because cerebral autoregulation is probably absent or failing. Future

intervention studies on blood pressure management during preeclampsia should also be aimed to ameliorate cerebral perfusion pressure and cerebral autoregulation.

Patellar reflex

It is common clinical practice to test patellar reflexes to establish neurologic agitation and to assess whether women with hypertension are at an increased risk to develop an eclamptic seizure. In our study on EMG quantification of the patellar reflex we only tested women with severe preeclampsia after stabilization (chapter 6). To our knowledge, this is the first study examining quantitatively the patellar reflexes during pregnancy and postpartum. Eventually, we had expected to find shorter latencies and higher amplitudes, but we were not able to confirm this assumption. Probably stabilization of the patients already decreased the peripheral agitation.

Although these results may suggest clearly limited clinical value of the patellar reflex in stabilized patients, it still may be useful to test patellar reflexes in non-stabilized patients. The latter has to be investigated.

Neuropsychology and Health related quality of life

In a neuropsychological study we showed that both short and long term memory is adversely affected in women after a previous severe preeclampsia. Our HRQoL study showed that especially social functioning and mental health are hampered in these patients. Since cerebral involvement during PE is especially present in the severe cases, the EEG abnormalities during preeclampsia may be explained by hypoxic events due to edema and/or aberrant perfusion. The resulting cerebral damage might be reflected in the cognitive disturbances that were diagnosed.

It is tempting to think that this cognitive impairment of the memory can, at least partially, explain the problems in daily life. Hoedjes et al. showed that formerly preeclamptic patients experience symptoms of post-traumatic stress disorder (PTSD) (20). Neonatal intensive care admission and perinatal death were other contributing factors to poorer HRQoL in these patients (21).

Baecke et al. published a study where they describe that cognitive complaints are common among young mothers, but PTSD is more common in preterm preeclampsia than in term preeclampsia and preterm birth (22).

The above-mentioned results in all of these studies are in line with studies in other fields of medicine, where they also find neuropsychological sequelae and impaired

health status after critical illnesses (23-27). Preeclampsia has to be considered as one of these critical illnesses leading to severe cognitive dysfunction.

Future research suggestions

Because preeclampsia can have such negative physical and mental effects on women's health, future studies should aim on preventive strategies. These strategies should focus on the prevention of preeclampsia and/or the prevention of the subsequent morbidity due to preeclampsia. In this respect, to improve maternal and fetal outcome in preeclampsia the timing of delivery has further to be optimized. In case of prevention of (imminent) cerebral damage one needs a reliable, easy to use measure, especially in the phase where the damage is still reversible and can be prevented.

Our new obstetrical unit at the Erasmus MC encompasses an obstetrical critical care unit where we are able to provide special care to severely ill pregnant women with cerebral and cardiovascular disease and their (often growth-restricted) fetuses. Both mother and fetus need dedicated multidisciplinary care of a specialized team. In this team perinatologists will work together with anesthesiologists, internal medicine specialists, neonatologists, cardiologists, neurologists and psychologists.

The interplay of hemodynamic and neurologic functions has never been investigated extensively. This large amount of information can be processed in the present era of computerization. In doing so, more insight into the relationship between all these parameters may be provided and contribute to the elucidation of the pathophysiology of preeclampsia. Continuous monitoring prevails over measuring random absolute values since it makes trends visible. Using trends instead of absolute values makes it possible to introduce personalized medicine. Continuous monitoring with new, easy and non-invasive methods to measure cerebral function should be developed. The close collaboration between the Erasmus MC and Leiden University Medical Center and the Delft University of Technology, formalized in the Medical Delta, may provide opportunities to develop these new techniques.

As also this thesis has showed, the psychological effects of severe preeclampsia are extensive. Women with severe preeclampsia more often deliver their babies prematurely. Both hospitalization of the baby and the neurocognitive sequelae of the mother will negatively influence their bonding (28). Currently, adequate programs to improve bonding between mother and baby are lacking. There is a strong need to develop and evaluate feasible programs which improve this aspect of motherhood.

Literature

1. Freathy RM, Mook-Kanamori DO, Sovio U, Prokopenko I, Timpson NJ, Berry DJ, et al. Variants in ADCY5 and near CCNL1 are associated with fetal growth and birth weight. Nat Genet. 2010;42(5):430-5.
2. Lin YS, Tang CH, Yang CY, Wu LS, Hung ST, Hwa HL, et al. Effect of pre-eclampsia-eclampsia on major cardiovascular events among peripartum women in Taiwan. Am J Cardiol. 2011;107(2):325-30.
3. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20(1):IX-XIV.
4. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99(1):159-67.
5. Gaugler-Senden IP, Duivenvoorden HJ, Filius A, De Groot CJ, Steegers EA, Passchier J. Maternal psychosocial outcome after early onset preeclampsia and preterm birth. J Matern Fetal Neonatal Med. 2012;25(3):272-6.
6. Furuta M, Sandall J, Cooper D, Bick D. The relationship between severe maternal morbidity and psychological health symptoms at 6-8 weeks postpartum: a prospective cohort study in one English maternity unit. BMC Pregnancy Childbirth. 2014;14:133.
7. Aukes AM, de Groot JC, Aarnoudse JG, Zeeman GG. Brain lesions several years after eclampsia. Am J Obstet Gynecol. 2009;200(5):504 e1-5.
8. Wiegman MJ, Zeeman GG, Aukes AM, Bolte AC, Faas MM, Aarnoudse JG, et al. Regional distribution of cerebral white matter lesions years after preeclampsia and eclampsia. Obstet Gynecol. 2014;123(4):790-5.
9. Johnson AC, Cipolla MJ. The cerebral circulation during pregnancy: adapting to preserve normalcy. Physiology (Bethesda). 2015;30(2):139-47.
10. Cipolla MJ, Sweet JG, Chan SL. Cerebral vascular adaptation to pregnancy and its role in the neurological complications of eclampsia. J Appl Physiol (1985). 2011;110(2):329-39.
11. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev. 1999;29(2-3):169-95.
12. Manfredi M, Beltramello A, Bongiovanni LG, Polo A, Pistoia L, Rizzuto N. Eclamptic encephalopathy: imaging and pathogenetic considerations. Acta Neurol Scand. 1997;96(5):277-82.
13. Sibai BM, Spinnato JA, Watson DL, Lewis JA, Anderson GD. Effect of magnesium sulfate on electroencephalographic findings in preeclampsia-eclampsia. Obstet Gynecol. 1984;64(2):261-6.
14. Johnson AC, Nagle KJ, Tremble SM, Cipolla MJ. The Contribution of Normal Pregnancy to Eclampsia. PLoS One. 2015;10(7):e0133953.
15. Belfort MA. Doppler assessment of retinal blood flow velocity during parenteral magnesium treatment in patients with preeclampsia. Magnes Res. 1993;6(3):239-46.
16. Belfort MA, Carpenter RJ, Jr., Kirshon B, Saade GR, Moise KJ, Jr. The use of nimodipine in a patient with eclampsia: color flow Doppler demonstration of retinal artery relaxation. Am J Obstet Gynecol. 1993;169(1):204-6.

17. Belfort MA, Saade GR. Retinal vasospasm associated with visual disturbance in preeclampsia: color flow Doppler findings. Am J Obstet Gynecol. 1993;169(3):523-5.

18. Belfort MA, Saade GR, Grunewald C, Dildy GA, Varner MA, Nisell H. Effects of blood pressure on orbital and middle cerebral artery resistances in healthy pregnant women and women with preeclampsia. Am J Obstet Gynecol. 1999;180(3 Pt 1):601-7.

19. Martin JN, Jr., Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol. 2005;105(2):246-54.

20. Hoedjes M, Berks D, Vogel I, Franx A, Visser W, Duvekot JJ, et al. Symptoms of post-traumatic stress after preeclampsia. J Psychosom Obstet Gynaecol. 2011;32(3):126-34.

21. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Steegers EA, et al. Poor health-related quality of life after severe preeclampsia. Birth. 2011;38(3):246-55.

22. Baecke M, Spaanderman ME, van der Werf SP. Cognitive function after pre-eclampsia: an explorative study. J Psychosom Obstet Gynaecol. 2009;30(1):58-64.

23. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson LV. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160(1):50-6.

24. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306-16.

25. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003;31(4):1226-34.

26. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJ, Carson SS, Curtis JR, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA. 2010;303(8):763-70.

27. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787-94.

28. Williams C, Patricia Taylor E, Schwannauer M. A Web-Based Survey of Mother-Infant Bond, Attachment Experiences, and Metacognition in Posttraumatic Stress Following Childbirth. Infant Ment Health J. 2016;37(3):259-73.

CHAPTER 9

Summary | Samenvatting

Summary

This thesis intends to describe and explain the course of clinical neurophysiological and neuropsychological parameters in patients with hypertensive disorders in pregnancy. We aimed to improve knowledge on cerebral pathophysiological mechanisms of pre-eclampsia related to signs and symptoms and to explore whether measuring features of these mechanisms with neurophysiological techniques can help to optimize timing of delivery in order to minimize maternal morbidity and maximize neonatal outcome.

A review on 22 articles (**chapter 2**) describe the electroencephalogram (EEG) during pre-eclampsia (PE)/ eclampsia. Abnormal EEG findings were observed in the majority of the pre-eclamptic/eclamptic patients, consisting of slow waves most frequently localized in the occipital lobe, as well as spike discharges. The EEG abnormalities in PE/ eclampsia were reversible in the majority of the cases. Most of the retrieved articles were published in the 1950s and 1960s and were not consistent with current clinical guidelines or medical terminology.

Therefore, we conducted our own study on EEG (**chapter 3**). We compared EEG findings during pregnancy and postpartum in women with normotensive pregnancies and pregnancies complicated by hypertensive disorders.

EEG's were recorded on several occasions during pregnancy and 6-8 weeks postpartum. Postpartum, the women filled out health related quality of life questionnaires. In women with severe preeclampsia significantly lower alpha peak frequency, more delta and theta activity bilaterally and a higher EEG Sum Score were seen. Abnormalities showed diffuse cerebral involvement and were not predominantly confined to the occipital areas. Postpartum, these women showed impaired mental health, mental fatigue and social functioning, which could not be related to the EEG findings. We concluded that women with severe PE show more EEG abnormalities and have impaired mental wellbeing postpartum, but these findings are not correlated.

In the next chapter (**chapter 4**) we present a study on visual evoked potentials (VEPs). VEP measure the functional neuronal integrity of the visual pathway from retina to the occipital cortex of the brain. The objective of this study was to compare neurophysiological changes in women with hypertensive disorders of pregnancy using VEPs. We defined reference values for normotensive pregnant women. Normotensive pregnant women had a shorter latency during pregnancy compared to their postpartum value. Women with severe preeclampsia had a prolonged latency of VEPs compared to normotensive pregnant women, a difference that disappeared postpartum. We concluded in this study that normotensive pregnant women show neurophysiological adaptation to pregnancy of their visual cortex, which seemed to be absent in women with hypertensive disorders of pregnancy.

Using Doppler ultrasound (**chapter 5**) we estimated zero flow pressure (ZFP) and cerebral perfusion pressure (CPP) using simultaneously obtained arterial blood pressure and middle cerebral artery blood flow velocity in women with preeclampsia, all treated with methyldopa ± nifedipine, and healthy pregnant controls. Mean ± SD ZFP was lower in patients than in controls whereas CPP was considerably higher, as was the cerebral flow index. There was a significant correlation between blood pressure and CPP in patients with PE, but not in controls. Women with PE may have an increased cerebral perfusion due to a reduced ZFP and increased CPP despite treatment with antihypertensive medication. More rigorous antihypertensive therapy, aimed at reducing CPP, could result in a decrease in cerebral complications in women with PE.

In normotensive pregnant women the patellar reflex was cross-sectionally recorded using surface electromyography at four time points during pregnancy and 6-8 weeks postpartum (**chapter 6**). In non-pregnant normotensive women this was recorded once. Preeclamptic women were recorded during pregnancy and postpartum. Latency and amplitude of the compound muscle action potential during normotensive pregnancies showed no changes compared to the non-pregnant state during reproductive age. Latency of the compound muscle action potential was increased in pregnancies with severe preeclampsia compared to normotensive pregnancies. Postpartum these differences had disappeared.

Women after PE more often complain of cognitive disturbances compared to women after uncomplicated pregnancies. We performed a study with a neuropsychological test battery in women who have had severe PE and women after uncomplicated normotensive pregnancies (**chapter 7**). The control group was matched for age, educational level and mode of anesthesia. All women delivered by cesarean section either under general or regional anesthesia. The formerly pre-eclamptic women had significantly lower scores on most indices of the auditory-verbal memory test. Formerly pre-eclamptic women learned considerably fewer words than controls and recalled less after interference. Study groups did not differ in parity. There were no differences in the level of intellectual functioning and language tests, such as naming and word fluency. No persistent differences were observed in tests for attention/concentration and executive functioning. There were no significant differences on depression and anxiety scales.

In **chapter 8** the general discussion reflects on limitations in our studies. It relates findings to clinical perspectives and suggestions for future studies are made.

Samenvatting

Dit proefschrift beschrijft en verklaart het verloop van klinisch neurofysiologische en neuropsychologische parameters bij patiënten met hypertensieve ziekten in de zwangerschap. Het doel is om onze kennis over cerebrale pathofysiologische mechanismen bij preeclampsie te verbeteren in relatie tot de symptomen. We willen onderzoeken of kenmerken van hypertensieve ziekten gemeten met klinisch neurofysiologisch onderzoek kan helpen bij het optimaliseren van het moment van de bevalling ten einde maternale morbiditeit te minimaliseren en neonatale outcome te maximaliseren.

Een review over 22 artikelen over elektro-encefalografie (EEG) bij (pre-) eclampsie wordt in **hoofdstuk 2** beschreven. In een groot deel van de patiënten met (pre-) eclampsie worden abnormale EEG bevindingen waargenomen, bestaande uit trage golven en pieken in voornamelijk de occipitaalkwabben. Bij een groot deel van de patiënten waren de afwijkingen reversibel. De gevonden artikelen waren van oudere datum (gepubliceerd in de jaren '50 en '60 van de vorige eeuw) en kwamen niet meer overeen met de huidige richtlijnen en er werd verlaten medische terminologie gebruikt. Hierdoor vonden we het relevant om een eigen studie over EEG te verrichten.

Deze studie wordt in **hoofdstuk 3** beschreven. We verrichtten een studie over EEG bij gezonde normotensieve zwangeren, bij vrouwen met chronische hypertensie en bij vrouwen met hypertensieve ziekten in de zwangerschap. We hebben de bevindingen van de EEG's vergeleken zowel tussen de groepen in de zwangerschap als met de postpartum bevindingen (6-8 weken postpartum). Verder vulden de geïncludeerde vrouwen postpartum een vragenlijst in met vragen over "health related quality of life". Bij vrouwen met ernstige preeclampsie werd er in de zwangerschap een significante lagere alfa piek frequentie, bilateraal een toegenomen hoeveelheid delta en theta activiteit en een toegenomen Sum Score gevonden. De gevonden afwijkingen kwamen bij ernstige preeclampsie diffuus door het cerebrum voor en niet voornamelijk in de occipitaalkwabben.

Post partum toonden deze vrouwen een verminderde mentale gezondheid, toegenomen mentale vermoeidheid en verminderd sociaal functioneren. Deze bevindingen correleerden niet met de gevonden EEG afwijkingen. We concludeerden dat vrouwen met een ernstige preeclampsie meer EEG afwijkingen en post partum een slechtere mentale gezondheid vertonen dan vrouwen in de andere onderzoeksgroepen.

In het volgende hoofdstuk (**hoofdstuk 4**) presenteren we een studie over visual evoked potentials (VEPs). VEP meet of de neurologische visuele banen van oog tot hersenschors intact functioneert. Het doel van deze studie was om de uitkomsten van VEP's te vergelijken tussen gezonde normotensieve zwangeren, vrouwen met chronische hypertensie en vrouwen met hypertensieve ziekten in de zwangerschap.

We hebben referentiewaarden voor gezonde normotensieve zwangeren gedefinieerd. Deze vrouwen toonden een kortere latentietijd tijdens de zwangerschap dan post partum. Vrouwen met ernstige preeclampsie toonden een verlengde latentietijd vergeleken met gezonde normotensieve zwangeren. Dit verschil verdween post partum. Hieruit concludeerden we dat gezonde normotensieve zwangeren een neurofysiologische aanpassing vertonen in de zwangerschap die niet aanwezig blijkt bij vrouwen die hypertensieve ziekten in de zwangerschap ontwikkelen.

In **hoofdstuk 5** hebben we met Echo-Doppler de zero flow pressure (ZFP) en cerebrale perfusiedruk (cerebral perfusion pressure (CPP)) bepaald door gelijktijdig de arteriële bloeddruk en de stroomsnelheid door de arteria cerebri media te meten bij vrouwen met preeclampsie en gezonde normotensieve zwangeren. Alle vrouwen met preeclampsie werden behandeld met methyldopa met of zonder nifedipine. De mean ± SD ZFP en de cerebrale bloedstroom index was lager bij patiënten met preeclampsie dan bij de gezonde normotensieve zwangeren.

Er was een significante correlatie tussen de bloeddruk en de CPP bij patiënten met preeclampsie; deze correlatie bestond niet bij de gezonde normotensieve zwangeren.

Het kan zijn dat vrouwen met preeclampsie een toegenomen cerebrale perfusie hebben door de afgenomen ZFP en de toegenomen CPP ondanks dat zij adequaat met antihypertensieve therapie worden behandeld. Bij de gezonde normotensieve zwangeren cross-sectioneel de kniepeesreflex gemeten met oppervlakte elektromyografie op 4 momenten in de zwangerschap en post partum (**hoofdstuk 6**). Bij de gezonde niet-zwangere vrouwen werd op een moment de kniepeesreflex gemeten. Bij vrouwen met preeclampsie werd de meting een keer tijdens de zwangerschap en een keer post partum gemeten. De latentietijd en de amplitude van de niet-zwangere en de gezonde normotensieve zwangere vrouwen toonden geen verschillen. De latentietijd van de vrouwen met preeclampsie was toegenomen ten opzichte gezonde normotensieve zwangere vrouwen. Post partum was dit verschil verdwenen.

Na een zwangerschap gecompliceerd door preeclampsie klagen vrouwen vaker over cognitieve problemen dan na een ongecompliceerde zwangerschap. Wij hebben een studie gedaan met neuropsychologisch onderzoek bij vrouwen na ernstige preeclampsie en na een normotensieve zwangerschap (**hoofdstuk 7**). De groepen werden gematched voor leeftijd, opleidingsniveau en soort anesthesie. Alle vrouwen in de studie zijn per sectio caesarea bevallen onder regionale of algehele anesthesie.

De vrouwen die een preeclampsie hadden doorgemaakt hadden significant lagere scores op de meeste indices van de geheugentest. Zij leerden aanzienlijk minder woorden dan de gezonde vrouwen. De groepen verschilde niet in pariteit. Het intellectueel functioneren verschilden niet tussen de groepen. Het taalgebruik was even vloeiden binnen de groepen. Er werden geen verschillen geobserveerd in de aandacht, concen-

tratie en executief functioneren testen. Er waren geen significante verschillen in depressie en angst.

In **hoofdstuk 8** wordt de generale discussie beschreven en wordt gereflecteerd op de problemen en beperkingen van onze studies. De bevindingen worden in klinisch perspectief geplaatst en er worden aanbevelingen gedaan voor vervolgonderzoek.

APPENDICES

List of Publications
Curriculum Vitae
PhD Portfolio
Dankwoord

List of Publications

1. **Brussé IA**, Duvekot J, Jongerling J, Steegers E, De Koning I. Impaired maternal cognitive functioning after pregnancies complicated by severe pre-eclampsia: a pilot case-control study. Acta Obstet Gynecol Scand. 2008;87(4):408-12. doi: 10.1080/00016340801915127. PMID: 18382865

2. **Brussé IA**, Peters NC, Steegers EA, Duvekot JJ, Visser GH. Electroencephalography during normotensive and hypertensive pregnancy: a systematic review. Obstet Gynecol Surv. 2010 Dec;65(12):794-803. doi: 10.1097/OGX.0b013e31821286f1. PMID: 21411024

3. Sonneveld MJ, **Brussé IA**, Duvekot JJ, Steegers EA, Grune F, Visser GH. Cerebral perfusion pressure in women with preeclampsia is elevated even after treatment of elevated blood pressure. Acta Obstet Gynecol Scand. 2014 May;93(5):508-11. doi: 10.1111/aogs.12358. PMID: 24754605

4. **Brussé IA**, Visser GH, van der Marel IC, Facey-Vermeiden S, Steegers EA, Duvekot JJ. Electromyographically recorded patellar reflex in normotensive pregnant women and patients with preeclampsia. Acta Obstet Gynecol Scand. 2015 Apr;94(4):376-82. doi: 10.1111/aogs.12580. Epub 2015 Feb 11. PMID: 25597232

5. van der Marel I, de Jonge R, Duvekot J, Reiss I, **Brussé IA**. Maternal and Neonatal Outcomes of Preterm Premature Rupture of Membranes before Viability. Klin Padiatr. 2016 Mar;228(2):69-76. Epub 2016 Feb 17. PMID: 26886145

6. **Brussé IA**, Duvekot JJ, Meester I, Jansen G, Rizopoulos D, Steegers EA, Visser GH. Electroencephalography in Normotensive and Hypertensive Pregnancies and Subsequent Quality of Life. PLoS One. 2016 May 11;11(5):e0155299. doi: 10.1371/journal.pone.0155299. eCollection 2016. PMID: 27167513

7. van Eerd DC, **Brussé IA**, Adriaens VF, Mankowski RT, Praet SF, Michels M, Langeveld M. Management of an LCHADD Patient During Pregnancy and High Intensity Exercise. JIMD Rep. 2016 Jun 23. [Epub ahead of print] PMID: 27334895

Curriculum Vitae

Ingrid Brussé werd geboren op 13 februari 1971 in Putte, Noord-Brabant. Na het behalen van het VWO diploma in 1989 volbracht zij de propedeuse Gezondheidswetenschappen aan de Rijksuniversiteit Limburg in Maastricht, thans Maastricht University. In 1990 startte zij op dezelfde universiteit de studie geneeskunde ernaast en behaalde haar artsexamen in 1997. Na twee jaar AGNIO (ANIOS) gynaecologie te zijn geweest (IJsselland ziekenhuis te Capelle aan den IJssel en Sint Franciscus Gasthuis in Rotterdam) startte zij in 2000 met de opleiding tot gynaecoloog in het academisch ziekenhuis Maastricht, thans Maastricht University Medical Centre Plus (MUMC+). In juli 2002 zette zij haar opleiding voort in de Rotterdamse gynaecologie opleidingscluster (RGOC) in het Sint Franciscus Gasthuis en het Erasmus MC, waarbij zij als eerste in Nederland een differentiatiejaar in de Perinatologie deed van 2004-2005. In 2006 startte zij met het Fellowship Perinatologie onder leiding van haar promotor (Eric Steegers) en co-promotor (Hans Duvekot). In het differentiatiejaar werd de basis van dit proefschrift gelegd, toen zij een pilotonderzoek naar EEG bij ernstige preeclampsie deed. In 2006 werd de ROBRA studie gestart, in samenwerking met de Klinische Neurofysiologie (co-promotor Gerhard Visser). Sinds 2008 is zij vast staflid Perinatologie in het Erasmus MC.
Ingrid is getrouwd met Rob Kusters en zij hebben samen twee kinderen, Merel (2005) en Daan (2007).

PhD Portfolio

1.PhD training	Year	ECTS
General academic skils		
Research Skills		
Introduction SPSS	2011	0.5
Principals of research in Medicine and Epidemiology	2008	1.0
Introduction to data analysis	2006	1.0
Seminars and workshops		
15th World Congress In Fetal Medicine, Palma de Mallorca, Spain	2016	1.5
25th World Congress on Ultrasound in Obstetrics and Gynecology, International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), Montréal, Canada	2015	1.5
19th World Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), New Orleans, USA	2014	2.0
13th World Congress In Fetal Medicine, Nice, France	2014	1.5
Advanced course: Fetal anomalies and CNS, International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), Amsterdam, Netherlands	2014	0.6
European Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), Tromso, Norway	2013	1.0
Obstetric Forum, Lisbon, Portugal	2012	1.0
11th World Congress In Fetal Medicine, Kos, Greece	2012	1.5
Global Congress of Maternal and Infant Health, Barcelona, Spain	2010	1.0
Course in Evidence Based Medicine, Eindhoven, Netherlands	2008	0.6
Wintercourse (NVOG), France	2009-2013	1.0
8th World congress of Perinatal Medicine, Florence, Italy	2007	1.0
Congresses of NVOG (Gynaecongres), Netherlands	2006-2016	1.5
Regional consortium Obstetrics (Bella Obstetrica), Rotterdam, Netherlands	2006-2016	3.0
Presentations at seminar		
Research meeting Erasmus MC	2006-2016	0.5
Regional consortium Obstetrics (Bella Obstetrica)	2006	0.5
Presentations at (inter)national conferences		
Obstetric Critical Care, symposium, *oral presentation*	2016	0.3
European Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), Budapest, Hungary, *oral presentation*	2015	1.5
European Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), Rome, Italy, *poster presentation*	2011	1.5
16th World Congress International Society for the Study of Hypertension in Pregnancy (ISSHP), Washington, USA, *poster presentation*	2008	1.5
15th World Congress International Society for the Study of Hypertension in Pregnancy (ISSHP), Lisbon, Portugal, *oral presentation*	2006	1.5
Congress of NVOG (Gynaecongres), *oral presentation*	2006	1.0
European Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), Rotterdam, Netherlands, *oral presentation*	2005	1.5
Congress, Society for Gynecologic Investigation (SGI), Los Angeles, USA, *poster presentation*	2005	1.5
Congress, European Chapter - International Federation of Clinical Neurophysiology, Stockholm, Sweden, *poster presentation*	2005	1.0

2. Teaching activities

Didactic Skills		
University Teaching Qualification (BKO)	2014	5.0
Class: Making exam questions	2012	0.2
Teach the teacher II	2009	0.5
Teach the teacher I	2008	0.5
Teaching		
Member Teaching Committee Medicine (EUR)	2009-2016	5.0
Member Teaching Committee Obstetrics & Gynecology (RGOC)	2015-2016	5.0
Lectures Obstetrics, School for Midwifery and School for Nurses (HRO)	2009-2016	3.0
Supervising Master's theses		
Clinical Obstetrics, A. Polat (HR0)	2014-2016	2.0
Medicine, W.H. Derksen (EUR)	2014	2.0
Medicine, I. van de Marel (EUR)	2012	2.0
Medicine, M.W. de Groot (EUR)	2011	2.0
Supervising practicals		
Clinical Obstetrics, A. Polat (HR0)	2014-2016	2.5
Medicine, I. van der Marel (EUR)	2014	1.0
Medicine, J.S. Erkamp (EUR)	2014	1.0
Medicine, M.W. de Groot (EUR)	2013	1.0
Medicine, N.C.J. Peters (EUR)	2010	1.0
Medicine, R.G. Boers (EUR)	2010	1.0
Mentorship of residents	2006-2016	2.0
Coaching of 4 bachelor medical students	2015-2016	0.3

3. Other activities

Fellowship Perinatology	2006-2008	5.0
Medical doctor, Department of Obstetrics and Gynecology, division of Obstetrics and Prenatal Medicine	2006-2016	5.0

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