Visual evoked potentials in women with and without pre-eclampsia during pregnancy and postpartum

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ABSTRACT

Objective

Pre-eclampsia is a severe hypertensive disorder of pregnancy which may lead to brain complications such as eclampsia. Visual symptoms are present in ~25% of pre-eclamptic women suggesting the visual cortex to be altered during pre-eclampsia. 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 pre-eclampsia and other hypertensive disorders of pregnancy, using VEPs. We hypothesized that women with pre-eclampsia and other hypertensive disorders of pregnancy develop abnormal latency and amplitude of VEPs as compared with normotensive pregnant women.

Methods

We performed a prospective observational study in 15 women with mild pre-eclampsia, 33 with severe pre-eclampsia (sPE), eight women with chronic hypertension, nine with pregnancy-induced hypertension, and 29 normotensive pregnant women. 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 sPE had a prolonged latency of VEPs compared with normotensive pregnant women (P = 0.006), a difference that disappeared postpartum.

Conclusion

Our study showed neurophysiological adaptation to pregnancy of the visual cortex in normotensive pregnant women, that seemed to be absent in women with sPE. The study groups of women with chronic hypertension and pregnancy-induced hypertension were too small to draw any conclusions from.

INTRODUCTION

About 2-8% of all pregnancies are complicated by pre-eclampsia (PE), a major cause of morbidity and mortality (1, 2). The mother's brain may be involved in pre-eclampsia (PE) and lead to severe brain complications such as eclampsia (3, 17). Brain complications may be the result of a disturbed auto regulatory response of the brain to increased blood pressure and endothelial cell dysfunction, which clinically presents as posterior reversible encephalopathy syndrome (PRES) (224). An elevated cerebral perfusion pressure may also predispose to cerebrovascular complications in pre-eclampsia (189). In addition, abnormalities on the electroencephalogram (EEG) are observed during this disorder (17). However, clinical evaluation of brain function during pre-eclampsia is not routinely performed that may help predict and/or prevent eclampsia in women with pre-eclampsia.

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 is likely localized in either the neurological or ophthalmic pathway (18). 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 (194). In addition, visual evoked potential (VEP) latencies decreases as gestation advances, suggesting adaptation of the visual cortex during pregnancy as well (225, 226). However, the functional status of the visual cortex during pre-eclampsia or hypertension in pregnancy that could lead to visual symptoms has not been investigated.

The objective of our study was to test neurophysiological function during pregnancy and postpartum by means of VEPs. We compared 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 (19). 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 (227). 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 the hypothesis longitudinally we studied these parameters during pregnancy and postpartum.

METHODS

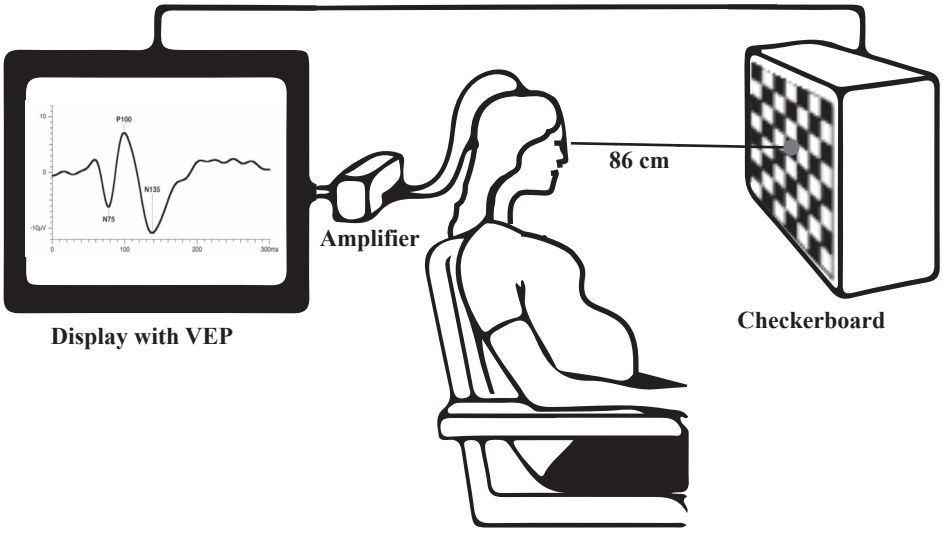
From October 2005 till July 2008 a prospective observational study was performed at the Department of Obstetrics and Gynaecology of the Erasmus MC University Medical Center in the Netherlands. Approval for the study was given by the Erasmus MC, University Medical Centre Research Ethics Board (MEC 2005-142). 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) (228). 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 (19). The VEP recordings were made in accordance with the 10-20 International System of Electrode Placement (229). 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 were 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

Figure 1. Image of a women 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).

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.

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.

In Figure 2 individual values of VEP latency and amplitude throughout normotensive pregnancy is shown. Because only a limited number of women with hypertensive disorders

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
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)	

** 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, NORM, normotensive pregnant women; CH, chronic hypertension; PIH, pregnancy induced hypertension; mPE, mild pre-eclampsia; sPE, severe pre-eclampsia*

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 pre-eclampsia; sPE, severe pre-eclampsia; ms, milliseconds; uV, microvolt.

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. 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.

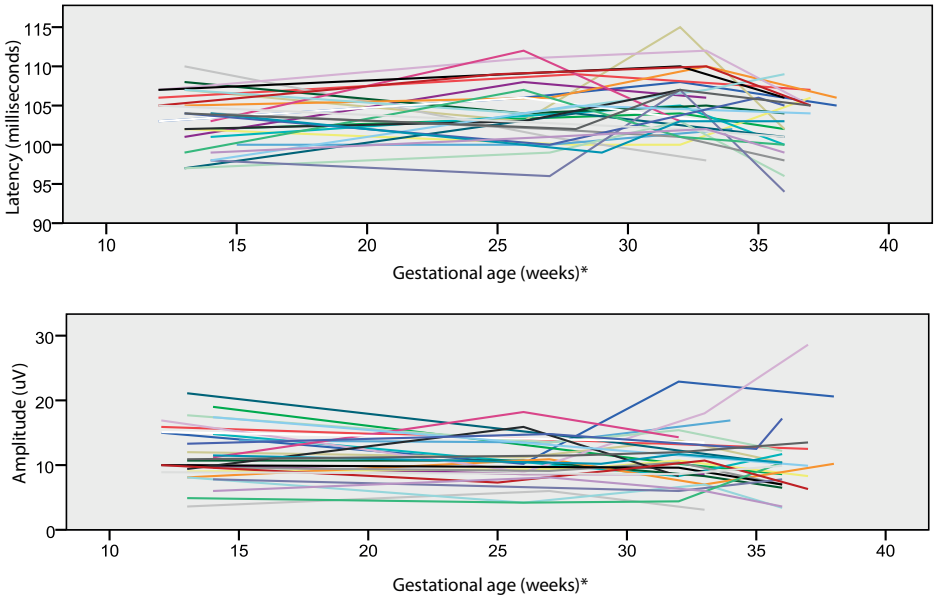
The latency upper limit, determined in the group of normotensive pregnant women was 110 milliseconds (ms) during pregnancy and 113 ms postpartum. The amplitude lower limit values were 3.4 microvolts (μV) during pregnancy and 3.9 μV postpartum. Figure 3 shows individual VEP latencies of the women in relation 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. Only in the group with severe PE a higher percentage of women showed 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 time 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.

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 pre-eclampsia; sPE, severe pre-eclampsia.*

Figure 2. VEPs in normotensive pregnant women

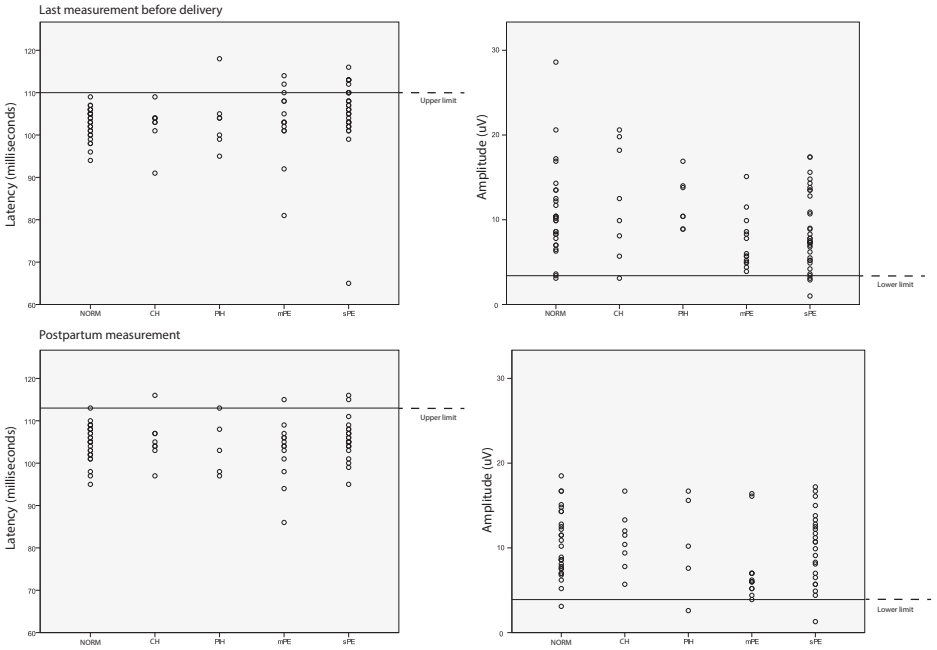


**Each line represents the course of the VEP during the pregnancy of an individual study participant*

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

Figure 3. VEPs during pregnancy and postpartum



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

is helpful in understanding the adaptation of the brain to pregnancy and hypertensive disorders. We determined reference values in normotensive pregnancy and postpartum. VEP latency and amplitude did not change during the course of normotensive pregnancy. Our results showed that a higher percentage of women with severe PE had VEP latencies above the normal values. Normotensive pregnant women had significantly shorter latencies during pregnancy compared to their postpartum measurements. From these findings we speculate that normotensive pregnant women experience physiological adaptation in pregnancy, while this adaptation fails in women with hypertensive disorders of pregnancy. This is also supported by findings of a previous study which described neurophysiological adaptations in pregnancy to preserve normalcy (230). It is hypothesized that pregnancy is a state with a higher neuronal network excitability and a lower seizure threshold (194, 230). However, other neurophysiological adaptations such as those occurring in the visual cortex, are largely unknown.

A 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 makes it difficult to draw any conclusions about women with CH and PIH.

There are few older studies available for VEP reference values in literature. The guideline of the American Clinical Neurophysiological Society on VEP refers to older published work as well (227). One of those studies produced reference values in only 19 healthy volunteers of both sexes (231). Another study categorized their reference values for age and sex, but included only ten women in the group in the reproductive age (232).

A study in 1991 compared ten third trimester pregnant women to non-pregnant women and found reduced latencies in the pregnant women. They concluded that pregnancy facilitates conduction process in the optic pathways (233). This supports our findings and hypothesis that normotensive pregnant women neurologically adapt.

Marsh *et al*. studied VEP in non-pregnant women, normotensive pregnant women and women with mild PE. They found a shorter latency in normotensive pregnant women compared to non-pregnant women. They did not find differences in latency and amplitude for normotensive pregnant women compared to women with mild PE (225, 226). 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 pregnancy. In contrast, this adaptation appears to be absent in women with hypertensive disorders of pregnancy, including pre-eclampsia. How this relates to visual symptoms that occur frequently in these patients is not clear. However, this adaptation can be assessed using neurophysiologic measurements including VEP. More research is needed to determine whether neurophysiological tests can predict severe neurological outcome in women with PE such as eclampsia.