Eclampsia & preeclampsia

Aukes, Annet Maria

Introduction

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Preeclampsia is a pregnancy induced disease, characterized by the occurrence of hypertension (systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg) and proteinuria in the second half of pregnancy in a previously normotensive woman. It complicates 5 to 7% of pregnancies in the United States.[1] It is a systemic disease of which the exact pathophysiology remains to be elucidated.

Preeclampsia is a systemic disease that can affect several organs including the liver, the kidneys and the brain. Involvement of the brain can lead to one of the most feared complications of preeclampsia: eclampsia. This is the onset of seizures or coma in a preeclamptic woman not attributable to any other cause. Accompanying symptoms are headache, visual disturbances (cortical blindness, scotoma, photopsia), photophobia, sonophobia, nausea, vomiting and altered mental status.[2] It is a life threatening disease for both mother and child and in the Netherlands cerebral complications such as eclampsia are responsible for most maternal deaths.[3]

The incidence of eclampsia in the Netherlands is 6.2 per 10,000 deliveries. The number of maternal deaths due to eclampsia is 1 in 74, fatality rate 1.4%.[4] Between 1993 and 2005 the maternal mortality rate of (pre)eclampsia in the Netherlands was 3.5 per 100,000 live births.[5] The major mode of maternal death due to hypertensive diseases is a cerebrovascular complication in 71% of the cases.[3] In other European countries the incidence of eclampsia is ranges from 2.4 to 5.0 per 10,000 deliveries[6,7] and ranging from 71 to 173 per 10,000 deliveries in developing countries.[8,9] The mortality rate from eclampsia in the UK is 1.8% [10], in the USA 0.5%[11] and ranging from 6.0-8.0% in developing countries.[9]

Why women with preeclampsia are susceptible to brain involvement is not clear. In addition, how pregnancy affects the brain is just being elucidated. Therefore, in our labs we investigate the brain during pregnancy in animal models and in patient studies we investigate the brain several years after a pregnancy complicated by eclampsia or preeclampsia.

Pathophysiology of eclampsia

There are two major theories on the pathophysiology of eclampsia, both based on failure of the cerebral autoregulation. One is the 'vasculopathy' theory which suggests that there is an 'overregulation' of the cerebral blood flow because previously it was thought that the neurologic symptoms of eclampsia were caused by ischemia. The theory behind this was that in reaction to acute hypertension the cerebral vasculature constricted too severely (overregulation of the cerebral blood flow) causing hypoxia and ischemia.

Evidence favoring this theory was the vasospasm seen on cerebral angiograms in some women with eclampsia.[12,13] Later newer imaging techniques showed presence of vasogenic edema, making ischemia as the only cause unlikely. More recently, Bartynski developed a more subtle theory based on the vasculopathy theory.[14] He hypothesizes that systemic toxicity in patients with (pre)eclampsia such as immune system activation, endothelial cell activation and injury, vascular instability and organ hypoperfusion, are associated with increased vasoconstriction of cerebral vasculature. The presence of systemic hypertension poses an additional trigger for vasoconstriction, leading to cerebral hypoperfusion and hypoxia. Prolonged hypoxia stimulates vascular endothelial growth factor (VEGF) release and activation of endothelial cells. Together, this may result in increased permeability of endothelium followed by vasogenic edema.[14] In support of this theory is the fact that vasogenic edema is typically found in the watershed zones. However, the suggestion that the cerebral vasculature would overregulate and constrict to such an extent to cause ischemia, seems unlikely. Therefore, we consider the second and currently more popular theory that focuses on loss of cerebral autoregulation, more plausible. In this theory it is hypothesized that in the presence of endothelial dysfunction an acute elevation of blood pressure exceeds the upper limit of the cerebral autoregulation leading to forced dilatation of cerebral arteries (Figure 1). Increased cerebral blood flow subsequently results in disruption of the blood brain barrier followed by extravasation of water and plasma solutes and formation of vasogenic edema.[15,16] Once the blood pressure decreases within normal limits of cerebral autoregulation, the vasogenic edema resolves and the neurological symptoms disappear.[17,18] Loss of cerebral autoregulation based on acute hypertension is called hypertensive encephalopathy. Eclampsia may be a form of hypertensive encephalopathy[19-21], however, not all patients with eclampsia have blood pressures high enough to reach the upper limit of cerebral autoregulation and 10% - 16% of eclamptic patients do not even become hypertensive.[10,11] In addition, a clinical and radiological condition similar to eclampsia has been recognized and is thought to be identical to eclampsia although the underlying triggering factor differs. This syndrome was first recognized by Hinchey et al. in 1996 and named 'reversible posterior leucoencephalopathy syndrome'.[17] Later, different names were introduced of which 'posterior reversible encephalopathy syndrome' (PRES) is currently most popular.[22,23]

Several aspects of the cerebral vasculature and its regulating mechanisms play an important role in the pathophysiology of eclampsia or PRES. In the following paragraphs the most important mechanisms of the cerebral vasculature will be discussed. These are cerebral autoregulation, the blood-brain barrier and perivascular innervation. The current knowledge about how these aspects are influenced by pregnancy will be discussed as well.

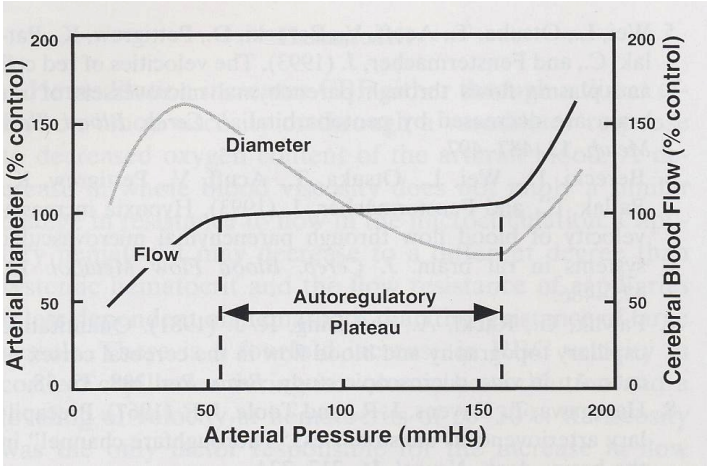

Figure 1 The cerebral autoregulation curve, adapted from Chillion and Baumbach 1997 and used with the permission of Elsevier Limited for Academic Press.[25]

Cerebral autoregulation

The term 'autoregulation' in relation to the cerebral circulation, was first introduced by Lassen in 1959.[24] Autoregulation of blood flow ensures that the blood flow through an organ is maintained at a relatively constant level despite changes in perfusion pressure or arterial blood pressure. Within the limits of cerebral autoregulation this is called the autoregulatory plateau (Fig 1), which ranges from approximately 50-60 to 150-160 mmHg in the healthy human.[25] This plateau is brought about by changes in the arterial diameter with vasoconstriction when blood pressure increases and vasodilatation when blood pressure decreases. When the mean arterial pressure is not within this range, autoregulation may be lost. In case of acute severe hypertension, such as in most cases of eclampsia, the cerebral arterial pressure exceeds the upper limit of autoregulation and cerebral blood flow increases linearly with increase in blood pressure.[26,27] Subsequently, the blood-brain barrier is disrupted and vasogenic edema develops.[15,16] When the blood pressure decreases, the cerebral blood flow normalizes and the edema resolves.[17-19]

Cerebral autoregulation is regulated by several control mechanisms.[28,29] One of those is the myogenic mechanism by which the small vessels react with constriction or vasodilation in response to changes in transmural pressure.[30,31] Secondly, there are metabolic mechanisms by which changes in metabolic demand of local brain areas during neuronal activity alters the cerebral blood flow in this area.[32] Thirdly, endothelium derived factors can regulate cerebral blood flow by exerting a constrictive or relaxing effect on the vascular smooth muscle. Vasodilatory factors are nitric oxide (NO), endothelium derived hyperpolarization factor (EDHF) and prostacylin, constrictor factors are thromboxane A_2,

prostaglandin $F_{2\alpha}$ and endothelin-1.[33] Finally, perivascular nerve activity may control cerebral autoregulation, which will be described below.

Chronic hypertension causes a right-shift of the cerebral autoregulation curve.[34] This is a protective effect, since loss of cerebral autoregulation on the upper end of the curve now occurs at higher pressures.[35,36] This right shift is caused by hypertensive remodeling and vascular hypertrophy, which normalize wall stress by increasing wall thickness and decreasing vascular diameter.[37-39] Stimulation of sympathetic innervation also results in a shift of the upper limit of the autoregulation plateau to higher pressures and has a protective effect on the blood-brain barrier.[40-42] In contrast, acute sympathetic denervation causes lowering of the upper limit of cerebral autoregulation.[43] During normal conditions the effect of sympathetic innervation on resting cerebral blood flow is minimal.[44]

Although progression is being made in this field, whether and how pregnancy influences the cerebral autoregulation has not exactly been elucidated. Some eclamptic women never reach blood pressures considered to be in the hypertensive range and therefore they do not necessarily reach the upper limit of cerebral autoregulation as this has been established in nonpregnant individuals. Thus, it seems likely that pregnancy shifts the upper limit or even the entire curve to the left and that hyperperfusion may occur at lower blood pressures compared to nonpregnant women. In vitro studies in late-pregnant rats showed that myogenic reactivity of posterior cerebral arteries was decreased and that the pressure at which forced dilatation occurs was lower in late-pregnant animals.[45,46] An in vivo study did not show a decrease of the upper limit of autoregulation in pregnant rats; there was no difference between late-pregnant and nonpregnant rats.[47] However, cerebral edema was more extensive in the late-pregnant animals after autoregulation breakthrough[47], suggesting that the blood-brain barrier is more vulnerable to disruption during pregnancy.

Blood-brain barrier

In the cerebral circulation, one of the most obvious and significant specializations is the formation of the blood-brain barrier by cerebral capillary endothelial cells. The endothelial cells in the brain's vasculature form high-resistance tight junctions through which there is no paracellular transport of water or solutes.[48] Also, endocytosis (transcellular transport) is minimal in capillaries of the central nervous system.[48] These features of the cerebral endothelium are considered the blood-brain barrier and protect the brain from formation of vasogenic edema. However, acute increased hydrostatic pressure may disrupt the blood-brain barrier with subsequent vasogenic edema formation.

It is important to understand how pregnancy influences the blood-brain barrier considering the fact that cerebral vasogenic edema is present in eclamptic and some preeclamptic patients.[49,50] In isolated cerebral arteries from rats, the vessels from late pregnant animals show increased permeability of the blood-brain barrier by increased endocytosis and paracellular transport when hydrostatic pressure is increased and forced dilatation occurs.[51,52] In an in vivo study, permeability to Evan's blue was increased after autoregulation breakthrough in late pregnant rats but there was no increase in permeability to sodium fluorescein.[53] Evan's blue permeability was greater in the posterior versus the anterior cerebrum suggesting regional differences in vulnerability of the blood-brain barrier, which may be an explanation for the regional distribution of vasogenic edema in eclampsia. Together, these findings suggest that pregnancy alters the permeability of the blood-brain barrier which may be important in case of acute hypertension.

Perivascular innervation

Cerebral vessels are associated with parasympathetic, sympathetic and sensory or trigeminal fibers.[28] They originate in cranial ganglia and distribute mainly to extraparenchymal vessels.[29] The autonomic neurons run through the adventitial layer of cerebral arteries in pial vessels ending in preterminal axons and terminals proper, which come in close contact with the outer smooth muscle layer of the vessel media.[29] This is the vasomotor innervation of both extracerebral and intracerebral small arteries and arterioles. Under normal resting conditions, perivascular innervation has little or no effect on cerebral autoregulation.[26,54,55] When the steady state of the cerebral autoregulation is altered such as in acute hypertension[55,56] or ischemia/reperfusion[57,58], perivascular innervation may influence the cerebral blood flow. However, the exact role on the regulation of cerebral autoregulation is controversial because of its complex nature.[58]

Cerebral vessels are innervated by an extensive sympathetic nerve supply.[59] In general, anterior vessels in the circle of Willis receive a denser sympathetic nerve supply than those in the posterior circulation.[59] Most of the pial arterioles are extrinsically innervated with sympathetic nerves originating from the cervical sympathetic ganglia.[60-62] Small pial vessels may receive intrinsic noradrenergic nerve fibers from the pons (locus ceruleus).[63] Under resting conditions, experimental manipulation of sympathetic input generally has little or no effect on cerebral blood flow in all the species examined, including humans.[29] However, during acute hypertension sympathetic nerves play a role in protecting the brain from autoregulation breakthrough and loss of integrity of the blood-brain barrier.[64,65] Stimulation of sympathetic nerves during acute hypertension attenuates the increase in cerebral blood flow.[42,55] In chronic hypertension sympathetic nerves exert

a trophic effect on cerebral vessels and contribute to hypertrophy of vascular muscle hereby protecting the downstream vessels.[66] The posterior brain is the primary site where autoregulation is overcome during acute hypertension and thus the primary site of vasogenic edema formation in eclampsia. One hypothesis is that this is because of the lesser sympathetic innervation posteriorly compared to the anterior cerebral vasculature, however, this hypothesis has not been proven.

Parasympathetic innervation plays a less well defined role in cerebral autoregulation. Parasympathetic fibers exert a dilator role, for example in ischemia/reperfusion.[58] In addition, cholinergic nerves interact with presynaptic noradrenergic nerve terminals and modify neurotransmitter release, for example by reducing the constrictor effects of sympathetic stimulation.[58]

Trigeminal innervation is mostly important in nociception, but also plays a role in cerebral vasodilation during cortical spreading depression[67,68], post ischemia/reperfusion[57] and on the lower end of the cerebral autoregulation curve.[69] Because of its role in migraine[70-74] – a disease that shares features with eclampsia[75-77] – and in vascular adaptation during pregnancy, the sensitivity and perivascular innervation of the trigeminal neuropeptide calcitonin gene-related peptide (CGRP) in cerebral arteries during pregnancy are a subject of this thesis.

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) is a neuropeptide of the sensory or trigeminal nervous system.[29,58,78] It is involved in modulation of peripheral vascular resistance[79-81], attenuation of gastric acid production [82] and nociception.[83] There are two isoforms of CGRP present, which are the α- and β-CGRP. The α-CGRP is a 37-amino-acid peptide produced by tissue-specific alternative splicing of the calcitonin/αCGRP RNA transcript.[78] It is located mostly at the central nervous system.[84] β-CGRP is produced from a different gene exclusive of alternative splicing and is mainly located in the enteric nervous system.[84] CGRP is co-located with substance P and neurokinin A in perivascular nerves where it transmits sensory information to the central nervous system, for example noxious stimuli, and where it serves a regulatory function of the local environment through the release of neurotransmitters.[29] CGRP containing perivascular nerves are found in many vascular beds throughout the entire body. CGRP is the strongest endogenous vasodilator known, in which the α-isoform has a stronger effect compared to β-CGRP.[79,84] The receptor that is identified as the CGRP receptor, is the calcitonin receptor-like receptor (CRLR). It is a G-protein coupled receptor and it requires binding to receptor activity modifying protein 1 (RAMP1) in order to become receptive to CGRP.[84,85] The signaling pathway can be either endothelium-dependent, endothelium-independent or both, differing per tissue bed and

species.[87] In the endothelium-dependent manner, CGRP can activate nitric oxide synthase (NOS), thereby releasing nitric oxide, causing vascular smooth muscle cell (VSMC) relaxation.[73,88] In the endothelium-independent pathway, CGRP binds directly on the CRLR/RAMP1 complex on the VSMC.[73,89] This activates adenyl cyclase, which in turn increases cAMP levels, causing VSMC relaxation.[73]

During pregnancy, levels of plasma CGRP increase to term and drop after delivery[90,91], suggesting that CGRP plays a role in the vascular adaptations that occur during pregnancy, when the plasma volume expands with 40% and blood pressure remains normal. In addition, plasma CGRP levels appear to be lower in the plasma of women whose pregnancy was complicated by preeclampsia compared to normotensive control women.[91] Plasma CGRP levels are also higher in pregnant rats compared to nonpregnant rats and the levels drop after delivery.[92] The vascular sensitivity to CGRP is greater in pregnant rats and ovariectomized rats treated with female sex steroid hormones compared to ovariectomized rats and male rats.[89,93] Administration of CGRP in pregnant rats treated with the NOS inhibitor L-NAME to cause preeclampsia-like features resulted in lowering of blood pressure, less fetal death and increased birth weight.[94] When the CGRP antagonist $CGRP_{8-37}$ was administered in L-NAME treated pregnant animals, blood pressure raised even further while there was no effect on blood pressure of untreated animals.[95] This effect was not associated with an increase of CGRP mRNA in dorsal root ganglia, suggesting that the underlying mechanism is an increased vascular sensitivity to CGRP during pregnancy. Together these findings suggest an important role of CGRP in maternal cardiovascular adaptations during pregnancy and that possibly CGRP or vascular sensitivity to CGRP is involved in the pathogenesis of preeclampsia.

Posterior Reversible Encephalopathy Syndrome

The occurrence of PRES is associated with several different conditions and progressively recognized in more and more different underlying pathologies. Most common patient categories are preeclampsia/eclampsia, patients treated with immunosuppressants or chemotherapy (e.g. cyclosporine and tacrolimus), malignant hypertension, infection/sepsis, solid organ or bone marrow transplantation and several autoimmune diseases.[17,96-98] The syndrome occurs at all ages, including the pediatric population.[99,100] There are no strict criteria, but diagnosis is made based on clinical findings and imaging. Symptoms of this syndrome are similar to eclampsia and include headache, nausea and vomiting, decreased alertness, altered mental functioning, seizures and visual disturbances such as blurred vision or cortical blindness.[17] These symptoms occur usually in conjunction with an acute elevation of the blood pressure.[17] Computed tomography (CT) shows localized hypodense lesions at the gray white matter junction or widespread

diffuse edema. However, occasionally focal areas of edema are beyond the resolution of CT scan, in which case magnetic resonance imaging (MRI) is necessary.[101] Findings on MRI are consistent with cerebral edema and include hypointensities on T1 sequence and hyperintensities on T2 and fluid attenuation inversion recovery (FLAIR) sequences.[17,98] The areas that are hyperintense on T2/FLAIR imaging are iso- or hypointense on diffusion weighted imaging (DWI) and hyperintense on apparent diffusion coefficient (ADC). This pattern of MRI abnormalities is consistent with vasogenic edema. The distribution of the edema on MRI is typically in the subcortical white matter of the parieto-occipital lobes and appears symmetrically. Although the name of the syndrome suggests indeed this kind of distribution, there is a wide variety. Atypical findings include edema in the frontal lobes, the inferior temporal-occipital junction, the cerebellum, the basal ganglia and brainstem.[97,98,102,103] Also, in some cases, the grey matter can be involved, the edema may be asymmetric or accompanied by hemorrhage. Moreover, DWI may demonstrate small areas of cytotoxic edema within lesions of vasogenic edema in patients with eclampsia.[104,105] In those instances it has been suggested that vasogenic edema in PRES can progress to such an extent that regional perfusion pressure decreases and blood flow decreases to ischemic levels leading to cytotoxic edema and infarction.[104,105] Imaging of obstetric patients with PRES (eclampsia and some cases of preeclampsia) is not distinct from other causes of PRES. In one study[106] the obstetric patients demonstrated more often involvement of the basal ganglia, however, this was not found in a larger study by Fugate et al.[98] Except for patients with hypertensive encephalopathy, hypertension is not always clearly present in all patients with PRES; 6 – 16% of PRES patients do not reach blood pressures commonly referred to as being in the hypertensive range.[11,97]

An abrupt rise in blood pressure undoubtedly contributes to the development of PRES but the exact underlying mechanism that causes disruption of the blood-brain barrier in this wide variety of patient categories, has not been elucidated. The conditions associated with PRES are typically systemic processes, which have some degree of endothelial dysfunction and an inflammatory response.[14] Possibly, these conditions (and other unidentified processes) predispose to an increased vulnerability of the cerebral vasculature to loss of cerebral autoregulation. This may be because increased permeability of the blood-brain barrier, a shift of the cerebral autoregulation curve to the left or both.

Animal models of (pre)eclampsia.

Preeclampsia and eclampsia are diseases that do not naturally occur in animals other than primates.[107] The ideal model of preeclampsia should include preferentially as many of the clinical and laboratory features of the disease as possible and progress to eclampsia-like symptoms if severe. However, such a model does not exist and therefore different animal

models of preeclampsia have been designed, some expressing the preeclamptic features more than others. Podjarny et al. gave a nice overview of animal models for preeclampsia including reduction of arterial blood flow to the uterus and placenta by aorta or ovarian artery clipping, chronic NOS inhibition with L-NAME administration or in an endothelial-NOS knock-out model, sympathetic nervous and/or renin-angiotensin system overactivation, inflammatory models with pro-inflammatory cytokine injection or injection of low-dose lipopolysaccharide, insulin resistance and models of angiogenesis antagonism with soluble fms-like tyrosine kinase 1 (sFlt1).[107]

Only a few studies focused on the brain when investigating preeclampsia models. Several models of hypertensive encephalopathy exist and have been used during pregnancy.[45,47] The systemic blood pressure can be increased acutely by administration of a pressor agent which causes loss of cerebral autoregulation. This has been done in our lab while cerebral blood flow was measured indirectly by laser Doppler[47] and with measuring microsphere content in different brain areas after autoregulation breakthrough.[19,108] Kanayama et al. described a rat model in which the celiac ganglion is stimulated with lipopolysaccharide in pregnant animals after which a preeclamptic and HELLP syndrome-like condition develops (Hemolysis, Elevated Liver enzymes, Low Platelets).[109] In addition, seizures occur, cerebral blood flow increases and cerebral edema develops.[110] Another model used in our lab is that of the Dahl salt-sensitive rat.[45] This rat becomes hypertensive when fed with a diet containing a high salt percentage (8%). At high blood pressures the Dahl salt-sensitive rat demonstrates symptoms similar to seizures of hypertensive encephalopathy: rhythmic, abrupt movements of the head in an up-an-down motion often associated with a lateral deflection or repetitive forearm flexion unilaterally.[111] There is evidence for disruption of the blood-brain barrier and edema formation in the brains of these rats as well as linearly decreasing myogenic reactivity with the duration of the high salt diet.[111] These rats also become hypertensive when fed a high salt diet during pregnancy[112] and demonstrate elevated markers of oxidative stress[113,114], both features of human preeclampsia. Furthermore, Dahl salt-sensitive rats suffer endothelial dysfunction, likely due to the salt-induced hypertension.[115] This model has one disadvantage: the Dahl salt-sensitive rats become symptomatic after 2.5 weeks of high salt diet, while the duration of pregnancy in rats is 3 weeks. However, it seems a good model for eclampsia and is used in Chapter 5.

Pressurized arteriograph system

The method that was used to investigate the effect of pregnancy, hypertension and different neurotransmitters on cerebral arteries *in vitro* in Chapters 5 and 6 is the pressurized arteriograph system. This system was developed at the University of Vermont,

United States, and is used extensively throughout the world to investigate vascular structure and function of small arteries and arterioles. In this experimental system, it is possible to investigate the effect of different pharmacological agents and physical forces such as pressure on the vascular smooth muscle and endothelium. The arteriograph that was used was a dual chambered system with two 20mL baths containing physiologic salt solution that is circulated to maintain temperature, oxygen, carbon dioxide and pH at physiologic levels. The carefully dissected vessels are mounted on two glass cannulas with nylon ties. The distal end of both of the cannulas is closed off to maintain pressure that is generated by a servo system that is connected to the proximal cannula. The servo system consists of a miniature peristaltic pump, an in-line pressure transducer and a controller. Through an optical window in the bath, the vessels are imaged by an inverted microscope that is connected to a video camera and a monitor. The video dimension analyzer (VDA) is used to analyze the signal obtained from the video image and to continuously register lumen diameter and wall thickness. The dynamic responses of vessel diameter and the intraluminal pressure are visualized on a computer by a serial data acquisition system that registers the VDA and pressure controller output, similar to a chart recorder. The cerebral autoregulation is subject to many different influences that cannot all be mimicked in an in vitro experiment. However, the use of the arteriograph system gives detailed insight into myogenic activity and passive structural properties of small cerebral arteries in response to some of the control mechanisms of autoregulation such as neurotransmitters and transmural pressure.

The maternal brain following eclampsia

It has long been thought that when a woman with eclampsia survives this condition without the occurrence of cerebral haemorrhage, she will fully recover.[116,117] This is plausible, because when the blood pressure decreases, cerebral vasogenic edema resolves. However, in addition to vasogenic edema also cytotoxic edema has been found during the acute phase of eclampsia.[105,118] Six to eight weeks post partum approximately one fourth of these formerly eclamptic women showed white matter lesions consistent with gliosis. How these lesions in formerly eclamptic women develop over life and their clinical relevance are unknown and are subject of this thesis. Moreover, some women with severe preeclampsia also demonstrated evidence of PRES on cerebral imaging even without experiencing eclamptic seizures[49,50] and an increased risk of stroke in formerly preeclamptic women has been reported.[119] Therefore, also formerly preeclamptic women are subject of neuroimaging and cognitive testing in this thesis.

Aims of this thesis

Part I (patient studies)

- To assess the long term consequences of preeclampsia and eclampsia on daily life with regard to cognitive function (**Chapter 2**)
- To provide insight into the long term consequences of eclampsia on the maternal brain with MR imaging (**Chapter 3**)
- To investigate the prevalence and severity of cerebral white matter lesions several years after preeclampsia and to find factors that are associated to these lesions (**Chapter 4**)

Part II (animal studies)

- To investigate whether decreased myogenic reactivity and the lack of hypertensive remodelling in cerebral arteries that occurs during pregnancy is due to the type of hypertension or to pregnancy (**Chapter 5**)
- To investigate the changes in cerebral perivascular innervation in different pregnancy-related states and the effect of gender on perivascular innervation (**Chapters 5 and 6**)
- To investigate the effect of pregnancy and gender on the sensitivity of cerebral arteries to sympathetic and trigeminal neurotransmitters (**Chapter 6**)

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Part I

Hoe
als je je
met zorgeloosheid
kon omringen
en dat dat
je ruimte
was

(Bert Schierbeek)