Summary

Chapter 1 Even though some progress has been made understanding its pathophysiology in the past decade, preeclampsia remains one of the most important unsolved problems in obstetrics. It is estimated that eclampsia causes 50-65,000 maternal deaths per year worldwide. Many women die due to cerebral complications such as intracranial hemorrhage. Pregnancy induces a multitude of rather profound physiologic hemodynamic alterations. However, the impact on cerebrovascular hemodynamic changes is largely unknown. The current management of preeclampsia relies on the paradigm that it evolves from mild to severe disease and then to eclampsia. This assumes that the more severe the symptoms, the more likely it is that a woman will develop an eclamptic seizure. It is, however, questionable whether this is a valid interpretation; seizures can not always be predicted by traditional measures as for example, the severity of the blood pressure. Little is known regarding the possible adaptation of cerebral autoregulation during healthy nor hypertensive pregnancy. Over the years, two major hypotheses regarding autoregulation of cerebral blood flow have evolved to explain the development of grand mal seizures in (pre)-eclampsia. The first theory emphasizes cerebrovascular “overregulation” resulting in extreme vasospasm and ischemia. The second hypothesis centers around a failure of cerebrovascular autoregulatory mechanisms to result in forced cerebral vasodilation. Ensuing cerebral hyperperfusion and vascular leakage result in subsequent development of reversible vasogenic edema. Clinically, this phenomenon of hypertensive encephalopathy has recently been coined Reversible Posterior Leucoencephalopathy Syndrome (RPLS). Both mechanisms can result in the development of cerebral edema, both with entirely different characteristics. This thesis utilizes modern MRI techniques to obtain more insight into the cerebral hemodynamics of normal as well as hypertensive pregnancy.

The circulation on and in the brain constitutes a unique vascular bed in several ways. Most importantly, the cerebral vasculature seems to be devoid of precapillary sphincters; the regulation of resistance across this vascular bed lies mainly in the arterial and arteriolar segments. The most well known difference between the cerebral vessels and the systemic vessels is the presence of the blood-brain barrier. The presence of the tight junctions is a distinguishing feature of the cerebrovascular
endothelium. The presence of hormonal effects on endothelium-dependent vasodilator production in the cerebral circulation indicates that pregnancy may be associated with alterations in the cerebral circulation that makes the brain more susceptible to forced dilatation and hyperperfusion during acute hypertension.

Chapter 1 subsequently presents the basic principles of MRI technology. MRI is based on the phenomenon of nuclear magnetic resonance (NMR) which originates in the nucleus of each atom. The reasons that these nuclei are NMR active derives from their property of nuclear spin; their intrinsic magnetic field. The proton at the center of each hydrogen atom possesses a magnetic spin. These spins can be manipulated by applied magnetic fields. MRI requires the application of carefully crafted magnetic fields that vary as precisely defined functions of space and time. All MR images will demonstrate signal intensity dependent upon so-called T1, T2-relaxation time and proton density. Contrast depends on these parameters as well as on tissue type. Liquor and hydrogen rich structures appear dark on T1-weighted images, whereas these appear white on T2 weighted images. Diffusion-weighted imaging (DWI) takes advantage of strong diffusion gradients to detect changes in water molecule distribution in cerebral tissue. The most exciting clinical application of diffusion imaging so far has been in the ability to detect hyperacute stroke. Quantitative measure of the diffusion property of a tissue is expressed as the Apparent Diffusion Coefficient (ADC). This technique differentiates reversible vasogenic cerebral edema (increased diffusion) from irreversible cytotoxic edema due to ischemia (reduced diffusion).

The cerebrovascular hemodynamics are extremely complex and governed by cerebral autoregulatory mechanisms as well as influenced by the physical properties of pulsatile flow of a complex fluid. In addition, the brain is unfortunately not easily accessible which explains why so little is known about the pregnancy-related changes in the cerebral circulation. The transcranial Doppler technique is the most widely used non-invasive modality to study the intracerebral circulation. This technique provides information on changes in cerebral blood flow velocities which, when combined with blood pressure, gives an index of cerebral perfusion and cerebrovascular resistance in the downstream arterioles. Unfortunately, for interpretation of Doppler indices like the pulsatility index, one has to rely on several assumptions before extrapolations about cerebrovascular resistance, can be made. These components are the inductance of the fluid, which is dependent on its
rheostatic properties and momentum, vascular compliance, which is related to the
elasticity of the vessel wall and the resistance to flow. Valid extrapolations regarding
vessel wall diameter and absolute blood flow are difficult to make as well. Multiple
studies in pregnancy have demonstrate a decrease in mean velocity in the middle
cerebral artery as pregnancy progresses. This is presumed secondary to decreased
vascular resistance, which could imply the presence of more distal arteriolar
vasodilation. In preeclampsia increased middle cerebral artery blood flow velocities
have been described. This rise in velocity is assumed to be secondary to high
resistance in the downstream arterioles. This observation has caused many over the
years to favor the vasospasm model for the etiopathogenesis of eclampsia. It is,
however, questionable whether this interpretation is valid.

More recently, velocity-encoded phase contrast MRI techniques have been
developed which do allow for accurate determination of absolute blood flow. This
method has been used to measure flow in the intracranial, renal and
cardiopulmonary circulations and has excellent correlation with traditional invasive
methods such as cardiac catheterization. The principle of this technique is the fact
that hydrogen nuclei in blood moving through a magnetic field gradient accumulate a
phase shift, which is proportional to their velocity. Blood flow is then calculated by
multiplying blood flow velocity and the cross sectional area of the vascular structure
of interest. SPECT (Single Photon Emission Computed Tomography) and
spectroscopy have also been used in a few studies to evaluate changes in regional
cerebral perfusion or metabolism, respectively, in healthy pregnancy as well as in
preeclampsia. The results are often conflicting, which illustrates the difficulty in
interpretation of the cerebrovascular mechanisms in preeclampsia.

Why the brain is preferentially involved in some preeclamptic patients is not
clear and will be a major question in preeclampsia research in the next decade.
Chapters 3 through 6 present preliminary work in this field and try to answer some of
the major questions. Even though the number of patients evaluated in these studies
may appear limited, in the context of the rare incidence of eclampsia they represent
sizeable studies the results of which are clinically important.
Chapter 2 reviews the neuroimaging findings of women suffering preeclampsia and relates these to the pathogenesis of cerebrovascular disturbances. Pubmed was searched from 1980 – 2004 using the key words “preeclampsia, eclampsia, computed tomography (CT), magnetic resonance imaging (MRI). All articles were subsequently cross-referenced. CT and MRI demonstrate transient lesions consistent with edema in the (sub)-cortical regions of the parieto-occipital lobes, basal ganglia and/or brainstem. Such lesions are thought to result from a failure of autoregulatory capacity with subsequent hyperperfusion and vasogenic edema. Under what circumstance this occurs is unknown. It does not necessarily seem to depend on the severity of hypertension. The presence of endothelial dysfunction as well as the magnitude of blood pressure change do seem to play a significant role. Eclampsia may represent the end stage of at least 2 different pathophysiological pathways; primary vasospasm versus forced vasodilation. When neuroimaging is desired using a series of MR diffusion sequences may further characterise the cerebral edema. On the basis of cerebral imaging findings attention has been directed to Reversible Posterior Leucoencephalopathy Syndrome (RPLS) as a model for the central nervous system abnormalities in eclampsia. The two conditions have many pathologic, radiologic, and clinical features in common.

Chapter 3 describes a prospective longitudinal study designed to evaluate cerebral blood flow during pregnancy and at six weeks postpartum in healthy women. This study provides physiologic normative data of cerebral blood flow (CBF) in two major regional arteries in both hemispheres. CBF was measured using velocity-encoded phase contrast MRI. Ten healthy pregnant volunteers underwent velocity-encoded phase contrast MRI at 3 time intervals: 14-16, 28-32 and 36-38 weeks’ gestation as well as at 6-8 weeks postpartum. Analysis consisted of serial paired Student t tests, with P<0.05 considered significant. By using these non-pregnant values for comparison. Cerebral blood flow decreased by 14-16 weeks’ gestation in the middle cerebral artery but was not significantly changed in the posterior cerebral artery. Flow then remained constant until 36 – 38 weeks’ gestation at which time there was another significant fall. Taken together, this represent a 20 % decrease in blood flow at term, compared to the non-pregnant situation. This was specifically caused by a
decrease in velocity and not by a change in large cerebral artery diameter. The posterior cerebral artery showed significant changes in flow only in women near term and not as early as the middle cerebral artery. These findings are in agreement with most studies in which velocities in the middle cerebral artery were determined employing transcranial Doppler ultrasound. The reasons for these changes in CBF in late pregnancy are unknown. One explanation for decreased CBF in the large cerebral arteries during pregnancy is generalized vasodilation of the downstream resistance vessels in the cerebral circulation to maintain a steady hemodynamic state. It is interesting to speculate that local autoregulatory changes in the cerebral circulation are due to altered vascular responsiveness or bioavailability of vasoactive mediators such as prostacyclin, nitric oxide and angiotensin-II as well as a variety of other substances such as Progesterone secondary to pregnancy. Alternatively or additionally, pregnancy may result in improved cerebral oxygen extraction capabilities.

Chapter 4 compares third trimester and nonpregnant cerebral blood flow in preeclamptic and normotensive women with the use of velocity-encoded phase-contrast MRI. Twelve patients who met the criteria for third trimester preeclampsia were recruited from the labor and delivery suite at Parkland Memorial Hospital before the onset of labor. These women as well as nine normotensive pregnant women underwent velocity-encoded phase contrast MRI to ascertain cerebral blood flow (CBF) in the posterior and middle cerebral arteries. Women with preeclampsia had a significantly increased CBF at term when compared with normotensive control subjects in the third trimester of pregnancy. This increase in CBF was not related to vasodilation of the major cerebral arteries because the diameter of these four main vessels was unchanged in women with preeclampsia. It is only speculative whether this increase is due to downstream vasodilation, increased cardiac output increased mean arterial pressure or local central nervous system factors of autoregulation.
Chapter 5 evaluates women with eclampsia using diffusion-weighted MRI techniques. This technique facilitates the discrimination between vasogenic and cytotoxic forms of cerebral edema. This issue is critical because the former implies reversibility and the latter implies cerebral infarction. The study included twenty-seven consecutive nulliparous women with eclampsia defined as new onset gestational hypertension accompanied by grand mal seizures. All women underwent T1 weighted, FLAIR, as well as diffusion-weighted MRI within 36 hours after convulsions. When evidence of cytotoxic edema was found women were asked to return six weeks postpartum for repeat MRI studies. Cerebral infarction was presumed to be present by the demonstration of persistent white matter lesions and evidence of gliosis on follow up MRI. All but two of these women (93%) demonstrated reversible vasogenic edema. These lesions typically, but not exclusively, involved the subcortical white and adjacent gray matter in the parieto-occipital lobes. Six were also found to have areas of cytotoxic edema consistent with cerebral infarction. Five of these six women had persistent areas of infarction when imaged postpartum, however, without gross clinical neurological deficits. In conclusion, the spectrum of cerebral lesions in eclampsia as seen with MRI varies from initially reversible areas of vasogenic edema that may progress to cytotoxic edema and infarction in up to a fourth of women.

Our findings confirmed that eclampsia, like other forms of hypertensive encephalopathy, usually develops with blood pressure well within the range in which autoregulation assures normal blood flow. Specifically, two-thirds of women now described had a mean arterial blood pressure of 120 mmHg or less.

Chapter 6 determines the effect of magnesium sulfate on maternal cerebral blood flow. Twelve preeclamptic women underwent velocity-encoded phase contrast magnetic resonance imaging studies before and immediately after infusion of a six gram magnesium sulfate loading dose. Cerebral blood flow was determined at the bilateral proximal middle and posterior cerebral arteries. Study participants returned six weeks postpartum to measure non-pregnant cerebral blood flow. There was no significant difference in cerebral vessel diameter nor cerebral blood flow for any of the examined arteries before or after magnesium sulfate therapy. In addition, when comparing non-pregnant vessel diameter and cerebral blood flow no difference was
found. In conclusion, the absence of a significant difference in cerebral blood flow of the middle and posterior cerebral arteries before and after infusion of a 6 gram loading dose of magnesium sulfate in women with preeclampsia could suggest the absence of vasoconstriction of the large cerebral arteries in preeclampsia and/or question the suggested role of magnesium sulfate as a vasodilator of these arteries.

**Chapter 7** The pathophysiology of Reversible Posterior Leucoencephalopathy Syndrome (RPLS) has been a source of extensive debate. Many investigators believe that the syndrome results from a disruption of cerebral autoregulation with subsequent areas of vasodilation, vasoconstriction and increased vascular permeability with extravasation of fluid into the brain parenchyma. The neuroimaging findings of eclamptic women, as described in chapter 3, are remarkably similar to those described in nonpregnant patients with RPLS. They also correspond with classic histopathologic studies of brain lesions in eclampsia described as cortical and subsortical edema, petechial hemorrhages and infarction. In addition, neuropathologic findings reported in non-pregnant individuals with fatal hypertensive encephalopathy resemble those described for eclampsia. In women with preeclampsia cerebral blood flow is increased over normotensive pregnant women. The increased cerebral blood flow in preeclampsia suggests a hyperperfusion model for cerebral edema instead of a primary vasospasm. Reasons are only speculative till now and include factors such as downstream vasodilation, increased cardiac output, increased mean arterial pressure or local central nervous system factors or other autoregulatory factors. Shear stress and changes in rythmic or pulsatile flow are known to be able to modulate the release of endothelial vasodilatory factors such as prostacyclin, nitric oxide or other endothelium-derived relaxing factors (EDRF) and endothelium-derived hyperpolarising factor (EDHF) all of which may play a role in modulating arterial complicance.

In conclusion, cerebrovascular events in preeclampsia appear to constitute a continuum characterized initially by increased cerebral blood flow. We hypothesize that, in conjunction with cerebral endothelial dysfunction, once a critical level is reached, a reversible phase of vasogenic edema and seizures occurs. Subsequently, in almost a fourth of women cytotoxic cerebral edema develops which results in irreversible areas of infarction, and ultimately, tissue loss. Although, in the past, these
infarctions have been attributed to vasospasm from cerebrovascular overregulation, we now hypothesize that vasogenic edema instead reduced cerebral perfusion to cause focal ischemia. This is likely because all areas of cytotoxic edema seen in our patients were encapsulated in areas of vasogenic edema. In this study MRI documents a transition between reversible vasogenic edema to irreversible cerebral ischemia and infarction in a fourth of patients. It is hoped that future advances in neuroimaging techniques such as specialised MRI modalities will aid our understanding of the etiopathogenesis of the neurological disturbances in preeclampsia.