Chapter 7.

Discussion, conclusions and future perspectives
Changing the eclampsia prevention protocol at Parkland Memorial Hospital in November 2000 formed the major impetus for this thesis. The “historic” intramuscular magnesium sulfate protocol for seizure prophylaxis in women with both mild and severe preeclampsia (Pritchard 1955) was changed into a more contemporaneous approach of restricting magnesium sulfate (solely the intravenous route) for seizure prophylaxis to only those women with severe preeclampsia (Williams 2005). Sometime after the implementation of the new protocol it became apparent that the incidence of eclampsia had tripled (personal communication). The recognition that several women were actually not diagnosed with preeclampsia prior to the occurrence of the eclamptic convulsion stimulated the investigation of the cerebrovascular hemodynamics and imaging in eclampsia. Subsequently, all women with eclampsia routinely underwent neuroimaging studies utilizing MRI, which resulted in the evaluation of several existing hypotheses; some outlined in this thesis.

Using such neuroimaging techniques it appeared that nearly all eclamptic women demonstrate specific cerebral lesions consistent with edema. The need to discriminate between vasogenic and cytotoxic forms of edema became apparent since the former implies reversibility and the latter implies cerebral ischemia and infarction. Simultaneously, the introduction of MRI techniques capable of making this particular discrimination (diffusion weighted MRI sequences) resulted in several case reports of different institutions in the world (Koch 2001, Kanki 1999, Schwartz 2000, Jurgensen 2001, Schaefer 1997, Schwartz 1998, Mukherjee 2001). It appeared that approximately 20% of eclamptic women described in such reports demonstrated evidence of irreversible cerebral lesions. This prompted the initiative for a systematic study to characterize the relative frequency of vasogenic and cytotoxic edema as well as the clinical characteristics of those patients (chapter 5).

Over the years, two theories have been proposed by several investigators to explain the cerebral abnormalities associated with eclampsia (see ch. 1). First, cerebral overregulation with vasospasm is thought to occur in response to acute severe hypertension. Alternatively, there is the theory of forced vasodilation; this is thought to occur in response to a breakthrough of cerebral autoregulation, hypertensive encephalopathy. Regardless of the mechanism the end result is cerebral edema which may be localised or generalised.

With this in mind, we became interested in cerebral blood flow patterns in women with preeclampsia. First, we aimed at elucidating basic physiology: what
happens to cerebral blood flow in normal pregnancy, and subsequently, in preeclampsia? Pregnancy-induced changes in cerebral blood flow were not studied before because accurate methods are either invasive or they require radioactive substances. More recently, several non-invasive MRI techniques such as velocity-encoded phase-contrast MRI developed which allows for accurate determination of absolute blood flow. This technique had been used extensively at the University of Texas Southwestern Medical School, particularly by several departments of cardiovascular medicine (Enzmann 1993, Marks 1992, Hundley 1995, 1996). These MRI techniques were employed to determine blood flow changes in the large cerebral arteries throughout normal pregnancy, during established preeclampsia, and to monitor the response of the large cerebral vessels to a loading dose of magnesium sulfate (chapters 3-6). The non-pregnant cerebral blood flow values in our studies appeared to correspond well with those values measured before in non-pregnant subjects (Enzmann 1993).

**Hypertensive encephalopathy and the cerebrovascular endothelium**

A unique aspect of the cerebral blood vessel endothelial layer is its function as the blood-brain barrier. A second function of cerebral endothelium is related to the modulation of vascular tone (Heistad 1992, Strandgaard 1984, Lassen 1973, Pavlakis 1999). Disruption or dysfunction of the blood-brain barrier can be produced by acute hypertension. It is believed that the autoregulatory mechanisms in response to increased blood pressure protect the brain from overperfusion. When severe experimental hypertension is induced by intravenous infusion of for instance angiotensin-II or norepinephrine, arterioles are shown to develop a pattern of alternating constrictions and dilatations, giving rise to the so-called “sausage string” appearance (Jacobsen 2002). This vascular pattern has been demonstrated in small blood vessels in various vascular beds including the brain. This phenomenon seems to be of a functional nature since it disappears on lowering of the arterial pressure and reappears when the pressure is rising again. In the microcirculation, the development of the sausage string pattern is linked to the development of vascular damage. Endothelial hyperpermeability and extravasation of macromolecules develop specifically in the dilated regions of the vessel. Jacobsen demonstrated that
the increased permeability observed in the dilated regions does not represent a simple pressure effect rather the increased permeability may represent an active endothelial response to the changes in the flow patterns and/or shear stress (Jacobsen 2002). Extrapolating to clinical practice, it has been shown that vasogenic cerebral edema may develop with only mild hypertension provided the presence of concomitant endothelial damage such as with hemolytic uremic syndrome, systemic lupus erythematosus, with immunosuppressive drug toxicity, or with the use of certain chemotherapeutic agents such as methotrexate (Lee 2004, Schwarz 1995, 1998, Port 1998). More recently, when this sequence of events develops one speaks of Reversible Posterior Leucoencephalopathy Syndrome (RPLS). The arterial boundary zones, located at the territorial limits of the major arteries are the predilected sites. These zones are originally termed the “border zone” or “watershed areas”. In the human, the most frequently affected region in the cortex is at the parieto-occipital sulci which represent the boundary zone of the anterior, middle and posterior cerebral arteries.

Previously, it was thought that cerebral vasospasm played a key role in the pathophysiology of cerebral symptoms in hypertensive encephalopathy. The misconception was that constricted segments of the vessels were undergoing extreme spasm. In contrast, the dilated segments are abnormal as these segments fail to maintain vasoconstriction, dilate passively and the blood-brain barrier in these segments disrupts. It is now thought that the constricted segments of sausage string arterioles are undergoing appropriate autoregulatory constriction instead of pathological vasospasm (Jacobsen 2002). Ischemic events do seem to occur; it is now hypothesized that this takes place when vasogenic edema becomes severe. In such instance marked local hydrostatic pressure results in decreased tissue perfusion and ensuing ischemia, which has been shown elegantly in animal studies (Tamaki 1984).
Is eclampsia a form of hypertensive encephalopathy?

The pathogenesis and pathologic, clinical and radiographic findings of RPLS are a reflection of the rapid and dynamic fluctuations in blood flow and water content of the brain that are characteristic of this disorder. Disruption or dysfunction of the endothelial blood-brain barrier appears to mediate the clinical picture. The characteristic permanent neuropathologic changes described when malignant hypertension was the cause for RPLS include fibrinoid necrosis and thrombosis of cerebral arterioles and microinfarctions and petechial hemorrhages in the basal ganglia, deep cerebral white matter and brainstem (Chester 1977, Healton 1982, Dinsdale 1983, Finnerty 1972). The neuroimaging findings of nonpregnant patients with RPLS are remarkably similar to those described in eclamptic women (Schwartz 1998). They also correspond with classic histopathologic studies of brain lesions in eclampsia described as cortical and subcortical edema, petechial hemorrhages and infarctions as well as neuropathologic findings of fatal hypertensive encephalopathy (Sheehan 1973).

On the basis of pathology and imaging findings as well as similarities in clinical presentation attention has been directed to hypertensive encephalopathy as a model for the cerebrovascular abnormalities in eclampsia (Schwarz 2000). Hypertensive encephalopathy (HTE) is the traditional term for the radiologic diagnosis of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) and used when this syndrome is particularly associated with acute severe hypertension. Strictly speaking, during a period of hypertensive encephalopathy, a relatively acute and excessive intravascular pressure increase causes forced dilation of intrinsic myogenic tone of cerebral arteries. This then decreases cerebrovascular resistance and increases pressure on the microcirculation thereby causing vasogenic edema formation. But, as stated in the prior paragraph, also in conditions with a relatively minor increase in blood pressure, but provided the presence of significant endothelial cell dysfunction, RPLS may occur. This may typically be the case in eclampsia as the myogenic vasoconstriction is overcome and causes loss of autoregulatory capacity in the microcirculation.

RPLS is an acute cerebral illness and may present with headache, nausea, altered mental function, visual disturbances and seizures (Hinchey 1996, Kinoshita 2003, Servillo 2003, Williams 1996). The convulsions are commonly, but not
exclusively, occipital in onset correlating with the characteristic predominantly posterior brain lesions noted on MRI. Recognizing RPLS is important because the neurologic disorder is readily treatable by correcting the underlying medical condition. It is now clear that other than the convulsions some patients with RPLS do not manifest the traditional prodromal cerebral signs and symptoms of hypertensive encephalopathy (Veltkamp 2000). In addition, there may be only mild to moderate but acute elevation in blood pressure, without the dramatic blood pressure increases that typify hypertensive encephalopathy (Bakshi 1998). In case of RPLS, the findings on MRI include focal white matter lesions superimposed on reversible generalized cerebral edema (Weingarten 1994). Such lesions in are usually isointense to hypointense on T1 weighted images and hyperintense on T2 weighted images, reflecting cerebral edema. Fluid-Attenuated Inverse Recovery (FLAIR) imaging, with nulling of the ventricular and subarachnoid CSF signal, is particularly useful in demonstrating the RPLS lesions. The abnormalities typically favor the posterior (parieto-occipital) white matter and corticomedullary junctions. However, involvement of the cerebral cortex may also occur in RPLS and lesions may extend to the brain stem, cerebellum, basal ganglia and more anterior brain regions such as the frontal lobes (Mukherjee 2001, Schwarz 1998, 1992, Ahn 2004). These atypical locations for RPLS make the syndrome sometimes difficult to distinguish from other disease of the brain that manifest with similar radiological characteristics, such as anoxic encephalopathy, infarction, extrapontine myelinolysis (EPM), or hypoglycemic encephalopathy (Ahn 1999).
Conclusions

1. An approximately 20 % reduction in large artery cerebral blood flow occurs during normal pregnancy, which is the result of a reduction in blood flow velocity, while the cross-sectional area of such vessels remains unchanged.

2. Large artery (the middle and posterior cerebral arteries) cerebral blood flow is significantly increased in severe preeclampsia. It is hypothesized that increased cerebral blood flow could ultimately lead to eclampsia through hyperperfusion and the development of vasogenic edema.

3. The lack of any statistically significant change in either diameter or flow of the large cerebral arteries after administration of a loading dose of MgSO4 may suggest the absence of vasoconstriction of cerebral arteries in preeclampsia. In addition, magnesium sulfate may not act as a large cerebral artery vasodilator. Alternative explanations, such as loss of autoregulation with subsequent development of vasogenic edema due to hyperperfusion, might better describe the pathogenesis of eclamptic convulsions.

4. 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.
5. Eclampsia may represent the end stage of at least 2 different pathophysiologic pathways; primary vasospasm versus forced vasodilation. When neuroimaging is desired the utilization of a series of MR diffusion sequences may further characterize the cerebral edema.

6. On the basis of cerebral imaging findings attention has been directed the Reversible Posterior Leucoencephalopathy Syndrome (RPLS) as a model for the cerebrovascular abnormalities in eclampsia. The two conditions have many pathologic, radiologic, and clinical features in common. The predominant feature is a relatively acute, more or less excessive rise in blood pressure, which causes forced dilation of cerebral arteries and arterioles, diminished cerebrovascular resistance, hyperperfusion and edema formation.

7. The discovery of new vasoactive processes mediated by the endothelium is ongoing and intruiging. Adding a further level of complexity, vascular smooth muscle cells are usually under the influence of multiple agonists at any one time. Many questions must be answered before such agonists can be considered a bona fide regulator of cerebral blood flow. For example: when is it functional? what is its physiological role? does it play a role in vivo during pathological states? What is its role in pregnancy?
Future research

Several areas of interest arise as the possible focus of future research:

1. Studies using Diffusion-Weighted MRI (DWI) of the cerebrum recently found that about a fourth of eclamptic women show irreversible ischemic changes (this thesis, Louirero 2003). The persistence of these lesions in the long term is unknown, but eclamptic women generally appear to have full clinical recovery. Recently, in a population study of migraine as a risk factor for subclinical brain lesions, it was reported that approximately 8% of people suffering repetitive migraine attacks versus 5% of the controls demonstrate T2 white matter lesions consistent with infarcts. It is now well known that such subclinical infarcts and white matter lesions in general are related to increased risk of adverse sequelae including clinical stroke events, physical limitations and cognitive impairment including dementia (Longstreth 1996, Vermeer 2003, Bernick 2001). Confirming the long term presence of infarctions in a substantial percentage of formerly eclamptic women over those with only preeclampsia or controls will have implications for current concepts of eclampsia as a disease: eclampsia should not be conceptualized as a solitary event but as a disorder with possible lifelong sequelae. With this shift in conceptualization the goals of treatment may also shift. Preventing the occurrence of eclampsia will be a more important goal than it is at the moment in treating women with preeclampsia, particularly if the brain lesions have a significant clinical correlate, which may deserve study in the near future as well.

2. There is a paucity of experimental data in higher order animal species and this is an important gap when extrapolating animal data to human subjects. For instance, there is a need to establish the cerebral blood flow autoregulatory curve in normal pregnancy. Following this, experimenting with the low/high end of this curve would be the next logical step.

3. Cerebral vasospastic hypoperfusion and vasodilatory hyperperfusion are hypothesized to be the 2 ends of the cerebral blood flow spectrum seen in preeclampsia. The coexistence of these two phases and the transition from one to
the other may explain why angiographically demonstrated spasm does not always relate well to cerebral blood flow and does not necessarily correlate with ischemia vice versa. The progression to subacute infarction in areas of cortical DWI hyperintensity is well known but the mechanisms by which vasogenic edema in Reversible Posterior Leukoencephalopathy Syndrome (RPLS) becomes cytotoxic remains an enigma (Covarrubias 2002). Animal studies show that in areas of massive vasogenic edema, increased tissue pressure eventually impairs the microcirculation and leads to irreversible ischemia (Tamaki 1984). Perfusion imaging techniques may be employed in order to make this distinction.

4. Currently, we are unable to discern which woman with preeclampsia is at risk for cerebrovascular complications. It may be that endothelial dysfunction may contribute to some of the major cerebral vascular complications. The possible relevance of cerebrovascular endothelial markers in preeclampsia should be sought after. Until then, we are unable to provide a rational therapeutic and preventive approach for the individual patient.

5. Endothelial factors may interrupt the delicate balance between capillary and cellular perfusion pressure. Basic laboratory sciences could focus on the functional and morphological changes in the cerebrovascular endothelium and the cascade of breakthrough of autoregulation, both in healthy pregnancy and in hypertensive disease. Considering the blood brain barrier it is important to examine the contribution of several potential pathways, the complementary use of genetically altered animal models, in vitro models and in vivo models using innovative pharmacological approaches.

6. Studies evaluating neurocognitive functioning before and after illness are not available. Such permanent cognitive changes might clearly be present but, so far, have gone unnoticed. The fact that most MRI findings are reversible does not prove clinical reversibility.

7. The possible pathophysiological implications of the relationships between sex hormones as well as a multitude of other endocrine modulators and cerebral hemodynamics deserve further investigation.
References


Port JD, Beauchamp NJ. Reversible intracerebral pathologic entities mediated by vascular autoregulatory dysfunction. Radiographics 1998;18:353-67

Pritchard JA. The use of the magnesium ion in the management of eclamptic toxemias. Surgery, Gynecology & Obstetrics 1955; 100:131-40


Strandgaard S, Paulson OB. Cerebral autoregulation. Stroke 1984;15:413-6

Tamaki K, Sadoshima S, Baumbach GL, Iadecola C, Reis DJ, Heistad DD. Evidence that disruption of the blood-brain barrier precedes reduction in cerebral blood flow in hypertensive encephalopathy. Hypertension 1984;6:75-81


