Chapter 1.

Introduction
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. Preeclampsia is relatively common: the average incidence of preeclampsia in the USA is estimated to be 26/1000 deliveries (Saftlas 1990). Eclampsia is defined as the development of convulsions and/or unexplained coma during pregnancy or postpartum in patients with signs and symptoms of preeclampsia (Sibai 2005). The word “eclampsia” is derived from Greek. It means a “flash” and is indicative of the fulminating character of the disease. Estimations of the average annual incidence rate of eclampsia in the USA is 0.43/1000 (Saftlas 1990), in the UK 0.49/1000 (Douglas 1994), and in Sweden 0.29/1000 (Moller 1986). Incidence rates in the Netherlands are currently unknown.

Along with hemorrhage, thromboembolism, and infection, preeclampsia is accountable for the world’s large maternal mortality rates. Many women with preeclampsia die due to eclamptic convulsions with or without ensuing intracranial hemorrhage. It is estimated that eclampsia causes 50-65,000 maternal deaths per year worldwide although the rates differ tremendously depending on the country in question (The Eclampsia Trial Collaborative Group 1995, Confidential Enquiries 2002). Between 1963 and 1979 the mortality rate for eclampsia in Mexico was 14 % (Lopez Llera 1992). This rate is similar in Nigeria during the period of 1972-1987 (Adetero 1989). Expectedly, in industrialised nations the eclampsia mortality rate is much lower but still significant. The eclampsia mortality rate in the Netherlands is estimated 2 - 2.8 % (Schuitemaker 1998). In the UK in 1992 the eclampsia mortality rate was 1.8 % (Douglas 1994), whereas in the USA eclampsia mortality rates of < 0.5 % have been reported (Sibai 1990, Pritchard 1984). In these countries eclampsia is the second leading cause of maternal death whereas in the Netherlands mortality due to hypertensive disease ranks first place representing 35 % of total maternal mortality.
Why does eclampsia occur?

Pregnancy induces a multitude of rather profound physiologic hemodynamic alterations. Among these are substantive increases in total blood volume, cardiac output and uterine blood flow (Williams 2005). However, the impact of pregnancy on cerebrovascular hemodynamic changes is largely unknown. Knowledge of possible pregnancy-induced alterations of cerebral blood flow could provide insight into abnormalities in cerebrovascular hemodynamics associated with preeclampsia. Over the years, two major hypotheses regarding autoregulation of cerebral blood flow have evolved to explain the development of grand mal seizures in preeclampsia. The first theory emphasizes cerebrovascular “overregulation” resulting in extreme vasospasm and ischemia (Lewis 1988, Ito 1995, Trommer 1988). The second hypothesis centers around a failure of cerebrovascular autoregulatory mechanisms to result in cerebral hyperperfusion and forced cerebral vasodilation. Ensuing vascular leakage results in subsequent development of reversible vasogenic edema. In the clinical setting this phenomenon has recently been coined Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES), or the more familiar term, hypertensive encephalopathy (Hinchey 1996). To complicate the potential sequence of cerebrovascular events in preeclampsia, frequently these scenarios occur despite a mild clinical picture and minimal elevation in blood pressure.

Pertaining to pregnancy, the blood pressure level at which cerebral autoregulation operates and possible deregulation occurs is unknown, but is likely to be variable. The systemic arterial pressure, intracranial pressure and many interdependent factors of the autoregulatory reflexes play an important role in determining cerebral perfusion at any given time. The critical threshold in relation to the onset of an eclamptic convulsion may well be related to the patient’s baseline blood pressure in addition to a more acute and rapid rise in blood pressure preceding the convulsion. This latter phenomenon is illustrated by the fact that at least in 16% of cases of eclampsia never reach a blood pressure of 140/90 mmHg prior to the convulsion (Mattar 2000, Douglas 1994).

The current management of hypertensive disease in pregnancy relies on the paradigm that preeclampsia evolves from mild disease 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. The most consistent prodrome of a seizure is severe throbbing headache. Other than headache fewer than half of the patients have signs or symptoms of preeclampsia before seizure onset (Katz 2000). Since most seizures can not be predicted by traditional measures other indicators need to be identified. Endothelial dysfunction is thought to play a key role in the clinical manifestation of preeclampsia (Roberts 1989, Taylor 1999). When this occurs in the cerebral circulation this is hypothesized to result in some degree of derailment of autoregulation and vascular leakage. Disease severity varies not only from patient to patient but also from organ system to organ system within an individual. Women with loss of cerebrovascular integrity may have seizures before the development of hypertension or proteinuria. Therefore, eclampsia is a cerebrovascular pathologic condition; it is not necessarily a condition of worsening hypertension and edema perse. What is unclear to date and a major area of future interest is which patient with signs and symptoms of preeclampsia will demonstrate evidence of altered cerebrovascular hemodynamics.

The Blood-brain barrier and cerebral autoregulation

The brain is a complex and heterogeneous organ that is critically dependent on its blood supply. The circulation on and in the brain constitutes a unique vascular bed in several ways (Edvinsson 2002). For instance, cerebral vessels have less smooth muscle and adventitia compared to the peripheral circulation. Cranial vessels beyond the dura mater have no vasa vasorum; in the peripheral circulation the vasa vasorum receives nutrients and disposes of waste products. Possibly, intracranial vessels receive nutrients directly from the cerebrospinal fluid (CSF). Interestingly, 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. In comparison with the peripheral circulation, which is well endowed with precapillary sphincters, this arterial system of resistance seems to be unique to the brain. Within the tunica intima at branching sites of arteries, however, the cerebral vessels express subendothelial protuberances. These consist of circumferentially arranged smooth muscle cells and collagen. Such sphincters are hypothesized to be
involved in the regulation of cerebral blood flow. Another difference is that in general, we consider large arteries to be conduit vessels and arterioles to regulate vascular resistance. It is suggested that this is not correct in the cerebral circulation and that, at least in the animal model, some larger caliber arteries upstream from small intracranial arteries appear to account for almost 50% of cerebrovascular resistance (Heistad 2001). Finally, the best known difference between the cerebral vessels and the systemic vessels is the presence of the blood-brain barrier (Heistad 2001). The blood-brain barrier is a dynamic structure capable of rapid modulations.

Impermeability is maintained by the microvascular endothelial cells through their tight junctions and basal laminae, which are composed of collagen, fibronectin, and various proteoglycans. The presence of such tight junctions is a distinguishing feature of the cerebrovascular endothelium (Huber 2001). A common feature of any type of lesion in this cerebrovascular endothelium is that it is always associated with the development of cerebral edema in the secondary phase.

The blood-brain barrier minimizes the entry of circulating catecholamines, hormones, ions and many other substances into the brain parenchyma and underlying vascular smooth muscle in order to ensure homeostasis of the neuronal microenvironment of the brain. When this barrier integrity is lost, inflammatory cells and fluid penetrate the brain, causing edema and cell death. Vasomotor tone changes profoundly during a wide range of changes in arterial blood pressure in order to maintain CBF at a relatively constant level. During acute and/or severe increases in arterial pressure CBF may, however, increase when so-called "breakthrough" of autoregulation occurs. This concept of vasodilation has been characterized as a passive phenomenon. However, increases in arteriolar diameter may not simply be a passive phenomenon but an active process that is mediated by calcium-dependent potassium channels and accompanied by the generation of reactive oxygen species (Heistad 2001). Stimuli that influence cerebrovascular tone and permeability characteristics generally fall into two main groups: the first includes all signaling entities that exert their effects through interaction with receptors populating the surface of the smooth muscle cells in cerebral arteries. Besides these receptor-dependent stimuli, a broad variety of other factors that influence cerebrovascular tone independent of direct interactions with cell surface receptors are observed (Pearce 2002). These include changes in intravascular pressure, blood...
gas tension or extracellular ion concentration. To make matter more complicated, such stimuli sometimes have opposite effects on the small and large vessels.

Despite these unique characteristics of the blood vessels supplying this extremely important organ, the cerebral circulation is quite understudied. For instance, the precise mechanisms by which changes in arteriolar and venular pressure contribute to disruption of the blood-brain barrier remain so far elusive. In the next paragraphs possible mechanisms involved in the physiological changes in CBF in pregnancy, as well as the pathophysiological changes in preeclampsia will be discussed.

**Hormonal influence on the cerebral vasculature**

**Menstrual cycle**

The interactions between estrogens and the cerebrovascular system are complex and not fully understood. There is evidence suggesting that the sex hormones confer protection against cerebrovascular disease; a lower incidence of cerebral ischemic events in women before menopause has been demonstrated, which rises in the postmenopausal period reaching values similar to those of men (Sivenius 1991). Estrogens are capable of influencing the adaptation capacity of the cerebrovascular system (Krejza 2004). This hormone seems to act at multiple sites in the brain and uses diverse signaling processes. The mechanisms of action of many substances in the brain or its surrounding vasculature, such as the sex hormones, can not be directly extrapolated from the mechanisms in peripheral vessels. For instance, the effects of estrogen on the endothelium-derived hyperpolarizing factor (EDHF) response in cerebral vessels are just the opposite of those reported in peripheral vessels (Golding 2002). Estradiol receptors are found in the endothelial and smooth muscle cells in the walls of brain arteries and arterioles (Stirone 2003). Stimulation of these receptors leads to relaxation of the microvasculature following the secretion of a variety of vasoactive substances such as nitric oxide (NO) and prostacyclin. Such compounds have a strong relaxing effect on the cerebral vasculature. In addition to acting indirectly via endothelial vasoactive substances,
Estrogens can directly reduce vascular smooth muscle tone by opening specific calcium channels. In addition, estrogen has a role in the density of the muscarinic receptors responsible for Acetylcholine-induced endothelium-derived relaxing factor release (Rainbow 1980). The changing levels of the sex hormones during the follicular and luteal phases of the menstrual cycle exert vasoactive effects on the intracranial cerebral circulation (Belfort 1995, Krejza 2004). Using transcranial Doppler in the late follicular phase when estrogen concentrations are 20-30 times greater than during menses, showed a decreased pulsatility index (PI) in the internal carotid artery. This supports a notion that estrogen-related promotion of CBF is caused mainly by a decrease in cerebral vascular impedance. The role of progesterone in the cardiovascular system is less well defined but it does appear to act as an antagonist to the effects of estrogen (Diomedi 2001, Krejza 2003, 2004). One proposed mechanism is that progesterone-mediated enhancement of respiratory ventilation during the luteal phase leads to a decrease in the concentration of PaCO$_2$, a well-known vasodilator within the brain. This subsequently increases vascular resistance in the microvasculature during the luteal phase.

**Pregnancy**

One of the best-known mechanisms involved in the regulation of cerebral blood flow (CBF) is a change in arterial carbon dioxide (CO$_2$) pressure. CO$_2$ has a strong vasodilatory effect on cerebral vessels, particularly on smaller pial arteries and arterioles. Using transcranial Doppler indices there seems to be increased downstream resistance to CBF within the MCA in the luteal compared to the follicular phase, a phenomenon that could be attributed to decreased alveolar CO$_2$ pressure subsequent to the progestagenic stimulus to ventilation (Brackley 1999). The markedly increased progesterone level concentration in pregnancy is also known to stimulate ventilation, starting already early in pregnancy (Spatling 1992). And, indeed, an increase in the standard Doppler indices from prepregnant follicular phase levels was already detectable by 4-7 weeks gestation in both the internal carotid and MCA, suggesting increased downstream resistance (Brackley 1998).
Pregnancy also affects endothelium-dependent vasodilator production in the cerebral circulation. This effect could significantly affect diameter regulation when the mean arterial pressure (MAP) is increased beyond the myogenic pressure range (Cipolla 2004). In other words, pregnancy may be associated with alterations in the cerebral circulation that makes the brain more susceptible to forced dilatation and hyperperfusion during acute hypertension. An elegant animal experiment suggests that the autoregulatory curve has indeed shifted to the lower ranges of pressures (Cipolla 2004); posterior cerebral arteries of late pregnant and postpartum rats dilated at significantly lower pressures that those from non-pregnant animals. For instance arteries of non-pregnant animals maintained significant tone at all pressures < 175 mmHg whereas arteries of late pregnant and postpartum animals already dilated at 146 and 162 mmHg, respectively. Because forced dilatation only occurs at pressures beyond the myogenic or autoregulatory pressure range, it is possible that during normal pregnancy, when blood pressure is normal, there is no consequence of attenuated pressure-induced reactivity. Only during pregnancy-related hypertension, when blood pressure at times may be relatively elevated, there is forced vasodilation and edema formation that may result in eclamptic convulsions.

There are several known contributors to forced dilatation that may be candidates for alteration during pregnancy; cerebral artery smooth muscle calcium-activated K+ channels which regulate arterial tone. Secondly, the state of actin polymerization in smooth muscle. Thirdly, altered endothelium-dependent vasodilator production such as nitric oxide and prostacyclin is likely to be involved as well. Lastly, pregnancy seems to upregulate Aquaporin-4, a water channel in the brain, which is related to edema formation (Quick 2005).
Other endocrine modulators of the cerebrovascular microcirculation

Stimulation of a variety of receptors on the endothelium can elicit dilatation of arteries and arterioles by initiating the synthesis and release of nitric oxide (NO) and/or metabolites of the cyclo-oxygenase pathway, in particular, prostacyclin. In the cerebral circulation, there is generally considerable basal nitric oxide production to mitigate myogenic tone, as is demonstrated by significant constriction in response to NO inhibition with \( \text{N}^\omega \text{-nitro-L-Arginine (L-NNA)} \) (Cipolla 2004). Recent evidence suggests that there are additional endothelium-dependent dilator factors that do not involve NO or a cyclo-oxygenase metabolite, and has been coined endothelium-derived hyperpolarizing factor (EDHF) (Golding 2002). EDHF is suggested to be a major regulator of cerebral blood flow (CBF) during physiological states and may become even more important following pathological insults such as ischemia. Unfortunately, very little is known regarding the identity of EDHF or its mechanisms of action in cerebral vessels. Sympathetic tonus is known to be markedly elevated in preeclampsia (Schobel 1996). It is not known what the influence is on the cerebrovascular circulation or whether this could be related to EDHF.

Many cerebrovascular diseases have an inflammatory component and it appears that the synthesis and release of cytokines may play an important role in alterations of the blood-brain barrier during disease states (Mayhan 2001). It has been suggested that various cellular mechanisms and multiple pathways be involved in this process. Functional studies have suggested that proinflammatory cytokines produce disruption of the blood-brain barrier via activation of the cyclo-oxygenase pathway. Eicosanoids induce endothelial upregulation of specific surface adhesion molecules (PECAM-1, E-selectin, ICAM-1) augment adhesion reactions, increase leucocyte migration and alter blood-brain barrier function (Mayhan 2001). Subsequently, the production of NO and expression of matrix metalloproteinases (MMPs) is increased (van Gasche 2001). MMPs are proteolytic enzymes that are able to digest the endothelial basal lamina leading to the opening of the blood-brain barrier, and are thought to play an active role in secondary brain injury after focal ischemia. Reactive oxygen species are implicated in blood-brain barrier disruption during stroke and it is suggested that these might participate in MMP activation and secondary alteration of capillary permeability (van Gasche 2001). Because free radicals are formed during normal cell activity the production is tightly controlled by
scavenging systems, including superoxide dismutase, glutathione peroxidase and catalase as well as by small molecules such as ascorbate, vitamin E and glutathione. There is substantial evidence to suggest that the phenomenon of oxidative stress (an imbalance in favor of oxidant versus antioxidant processes) plays an important role in the cycle of events that compromise the vascular endothelium in preeclampsia (Hubel 1999).

**MRI technology**

MRI was introduced as a clinical modality about ten years after computed x-ray tomography (CT) became an established diagnostic tool. During the 1980’s engineering advances combined with newly developed scientific and clinical understanding produced this completely new addition to the medical diagnostic armamentarium. Since the early 1990’s efforts have been aimed at improving the effectiveness and reducing the costs of MRI and at the development of new applications to extend the range of its usefulness (Atlas 1996).

MRI is based on the phenomenon of nuclear magnetic resonance (NMR) which originates in the nuclei of atoms. The reasons that these nuclei are NMR active derives from their property of nuclear spin; their intrinsic magnetic field. The spinning proton creates a magnetic moment so that it behaves like a simple bar magnet. The proton at the center of each hydrogen atom possesses a magnetic spin. These spins can be manipulated by applied magnetic fields. Signals produced by the motion of the spins can be detected outside the body. MRI requires the application of strong and carefully crafted magnetic fields that vary as precisely defined functions of space and time. Magnetic fields are often produced by passing a current through a coil of wire which, by using a large number of turns, makes it possible to produce a strong field using only a relatively modest current. Every MRI scanner contains several sets of coils which serve as sources of the magnetic fields to manipulate the magnetic spins within the patients. Three gradient coils are required to permit slice selection. Activating 2 or all 3 of the gradient coils simultaneously can generate a gradient in any arbitrary direction. This makes it possible to select imaging planes in any one of the principal orientations, axial, sagittal or coronal and also in any oblique orientation. This flexibility to select any desired scan plane electronically and without
moving the patient gives MRI one of its major advantages over CT and other imaging modalities. By placing any substance within an external magnetic field, the orbital motion of the electrons will be altered so as to induce a net magnetic field within the substance. When equilibrium is achieved the net magnetization of a collection of protons points along the direction of the external magnetic field even though the magnetization of each individual proton is at an angle with respect to this field. When a collection of protons (for instance a patient) is initially placed in this external magnetic field, the time required to achieve equilibrium is called T1 relaxation time and depends on the tissue type as well as whether the protons are in water or lipid. The T2 relaxation time of a tissue is a measure of how long magnetization persists once the magnetic field pulse is turned off before returning to the equilibrium situation. All MR images, regardless of the parameters chosen, will demonstrate signal intensity dependent upon T1, T2 and proton density. However, depending upon the choice of Repetition Time and Echo Time one parameter can be made to dominate the signal intensity characteristics. Hence the term “weighted” is used. This basically determines contrast.

**Diffusion-weighted MR imaging**

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 (Chien 1992, Warach 1995). Quantitative measure of the diffusion property of a tissue is expressed as the Apparent Diffusion Coefficient (ADC). In the presence of infarction, cerebral edema is caused by sodium pump failure and the resultant reduction in proton diffusion elicits hyperintense (bright) signal on DWI. This form of edema is called cytotoxic edema (Edvinsson 2002). Diffusion changes are seen within minutes of the onset of ischemia; this is much earlier than with standard MRI sequences since these are only sensitive to acute ischemic changes hours after the insult. The time-course of diffusion imaging of stroke shows that the apparent diffusion coefficient (ADC) decreases about 40 % during the first minutes after the acute insult. The ADC reaches its low point after 2-4
days. Following this, the ADC begins to climb and reaches the signal intensity of normal tissue about 7-10 days after insult (Chien 1992). Conversely, the other form of cerebral edema, i.e. vasogenic edema, is the result of vascular leakage or hyperperfusion. This is characterized by increased extracellular fluid with enhanced water diffusion and may be seen as normal or decreased signal brightness on DWI (Engelter 2000). In some cases of vasogenic edema, however, hyperintense signal may be seen on DWI, dubbed “T2 shine-through” (Burdette 1999). Thus whether DWI hyperintensity is due to restricted diffusion or to T2 shine-through is a potential diagnostic difficulty. This issue is resolved by estimation of the underlying ADC of the tissue in question. Because the ADC calculation is independent of T2 effects it determines whether diffusion is restricted or unchanged in the area of interest. A decreased ADC that corresponds to hyperintense areas on the DWI represents restricted diffusion. In contrast, elevated ADC represents water molecules with increased diffusional motion and thus vasogenic edema.

**Techniques to evaluate cerebral hemodynamics in preeclampsia**

The circle of Willis is the anastomotic ring at the base of the brain distributing blood flow regionally to the cerebral cortex. The internal carotid and vertebral arteries, which unite intracranially as the main source of blood flow to the brain, supply the circle of Willis. After exiting the circle of Willis, the paired anterior, middle and posterior cerebral arteries branch to form a network of arterioles and capillaries. The hemodynamics of this vascular network are extremely complex and governed by cerebral autoregulatory mechanisms as well as influenced by the physical properties of pulsatile flow of a complex fluid. The middle cerebral artery carries nearly 80% of the flow to the hemispheres of the brain and is the artery responsible for the majority of parietal lobe blood flow. These paired blood vessels have special significance in preeclampsia because eclamptic seizures generally manifest with motor abnormalities in a distribution consistent with parietal lobe electrical disturbance.

The increase in cardiac output observed during normal gestation results in a remarkable increase in blood flow, which is distributed among several maternal organ systems (Rosenfeld 1977). The uteroplacental blood flow demonstrates a 10-fold increase in blood flow (Gant 1989). Blood flow to the kidneys increases with
approximately 50% over non-pregnant levels by mid-gestation (Dunlop 1981). The breasts and skin also receive more blood flow compared to the nonpregnant state (Parisi 1992). Despite the increase in cardiac output during pregnancy hepatic blood flow has been reported in one small study to be relatively unchanged (Munnel 1947). Knowledge of pregnancy-related physiologic changes in cerebral blood flow is virtually non-existent compared with our knowledge of the alterations in other vascular beds. This is partly due to technical difficulties associated with in vivo studies of blood flow in the human brain. In 1949, McCall first reported on cerebral blood flow in normal pregnant women and in women with eclampsia. An inhalation technique of a gaseous mixture containing nitrogen, nitric oxide and oxygen was utilized. Internal jugular arterial and venous blood was then collected and the Fick principle applied by measuring serum concentrations. This study demonstrated that in eclampsia the delivery of oxygen and CBF were normal but there was a 20 % decreased utilization of oxygen by the eclamptic females. Obviously, there are ethical and logistic problems involved in such studies as there are with angiography or other techniques involving radioactive tracers during pregnancy. For unknown reasons, little work in animals has been done either. Some techniques, capable of examining at least part of the cerebrovascular hemodynamic system, will be discussed in subsequent paragraphs.

**Transcranial Doppler Ultrasound**

The transcranial Doppler technique is the most widely used non invasive modality to study the intracerebral circulation, first in neurosurgical patients for the early detection of cerebral vasospasm following subarachnoid hemorrhage (Giller 1998, Hatab 1997), later also in obstetrics, particularly in the field of hypertensive disorders of pregnancy (Belfort 2001 thesis). Transcranial Doppler (TCD) studies of the central nervous system determine the velocity of red blood cells flowing in the middle cerebral artery (MCA). 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 (Aaslid 1992). Resistance to flow in an artery is inversely proportional to the 4th power of vessel radius when laminar flow occurs and the flow is in steady
state. Although in physiologic systems steady state flow is probably never achieved, it is reasonable to assume that microvascular constriction significantly increases the resistance met by blood inflowing from arteries supplying the microvasculature (Burns 1988). Cerebral perfusion pressure (CPP) is the difference between the mean arterial pressure and the intracranial pressure and is the main determinant of brain perfusion. CPP is increased in women with severe preeclampsia when extrapolated using TCD (Belfort 2002). Using TCD one has to rely on several assumptions in making extrapolations regarding vessel wall diameters and absolute blood flow. Any of the components of impedance in a nonsteady state system can affect both the peak systolic and end diastolic velocities required for calculation of the pulsatility index. 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. Vascular compliance results from the ability of the vessel wall to stretch in response to increased intraluminal pressure. It is a major contributor to the overall vascular impedance in the pulsatile flow system (Krejza 2003). An increase in compliance can increase impedance indices without changes in vascular resistance.

Multiple studies, both longitudinally as well as cross-sectionally in healthy pregnancy have demonstrated a decrease in mean velocity in the MCA as pregnancy progresses (Belfort 2001, Williams 1994, Serra-Serra 1997, Demarin 1997, Ikeda 1991). This is presumed secondary to decreased vascular resistance, which could imply the presence of more distal arteriolar vasodilation. Several investigators employing this technique in preeclampsia have shown increased middle cerebral artery blood flow velocity in women with preeclampsia (Ohno 1997, Zunker 2000, Williams 1998, Demarin 1997, Williams 1994). Preeclamptic women with visual disturbances and/or headache demonstrate the highest velocities (Ohno 1997, Belfort 1999). The same is true for women with eclamptic seizures (Will 1987, Trommer 1988, Ohno 1999, Williams 2003, Naidu 1997, Ringer 2001, Qureshi 1996, Vliegen 1993, Williams 1993, Hashimoto 1997). 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 (Belfort 1999, 1999, 2001, Williams 2003, 1993). But whether elevated MCA velocity indicates ischemia or hyperemia is unclear since high MCA velocities can occur in both situations (Romner 1996). Depending on where the MCA is
insonated a high mean velocity may be found in both vasospasm and vasodilation because of the combined dynamic and segmental changes in vessel wall caliber in (pre)-eclampsia. Again, drawing conclusions using cerebral blood flow velocity info alone can, therefore, be misleading. Cerebral blood flow velocity seems reduced by antihypertensive therapy (Serra-Serra 1997) and magnesium sulfate (Belfort 1992, 1993). This has been ascribed to relieve of cerebral vasospasm (Belfort 1992, Naidu 1996), but this also remains speculative.

Dynamic cerebral autoregulation testing using a non-invasive approach was recently described in preeclampsia (Oehm 2003). Such technique is based on the response of cerebral blood flow velocity to small physiological changes in arterial blood pressure. For example, using stimuli with CO\textsubscript{2} increases cerebral blood flow velocity unless the capacity for cerebral vasodilation is exhausted. Studying eclampsia revealed a diffuse loss of cerebral autoregulation with widely preserved vasomotor reactivity. It suggests a serious impairment of the autoregulatory feedback mechanisms.

**Velocity-encoded phase contrast MRI**

More recently, magnetic resonance imaging techniques have been developed that do allow for accurate determination of absolute blood flow. Velocity-encoded phase contrast MRI has been used to measure flow in the intracranial, renal and cardiopulmonary circulations (Enzmann 1993, Marks 1992, Hundley 1995, 1996). The method has excellent correlation with traditional invasive methods such as cardiac catheterization and the Fick principle and the thermodilution technique (Hundley 1995). The measurement of blood flow in the intracerebral vessels is accurate with this method because the magnetic resonance technique offers high spatial resolution for vessel localization and cross-sectional area measurement (Morris 1997). 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 (Figures 1-4).
**Single Photon Emission Computed Tomography (SPECT)**

SPECT involves intravenous injection of a radioisotope and affords the opportunity to assess alterations in regional cerebral blood flow. The effect of early pregnancy on maternal regional cerebral blood flow was assessed in women with planned abortions between 7 and 19 weeks’ gestations. Regional CBF in the cerebral frontal temporal and parietal lobes as well as in the basal ganglia and cerebellum, decreased in the postabortion period with about 10% compared with CBF during pregnancy. There was no significant difference in blood flow in the occipital lobe before versus after the abortions (Ikeda 1993). SPECT in patients with reversible posterior leuco-encephalopathy syndrome (RPLS) secondary to renal disease demonstrate increased regional perfusion to edematous occipital lobes of the brain, whereas acute ischemia is generally associated with decreased perfusion (Schwartz 1992).

Only two reports utilizing this technique in preeclampsia were found. Apollon (2000) used SPECT in a woman with preeclampsia and cortical blindness and showed hyperemia in the posterior, temporal cortex, lateral occipital cortex and inferior parietal cortex. These lesions were more extensive compared with conventional MRI. Eight days later there was complete recovery. This seems to correspond with the findings in non-pregnant patients with RPLS. Using a similar method, Xenon CT, diffuse cerebral hyperperfusion and vasogenic edema without evidence of vasospasm was demonstrated in women with eclampsia (Ohno 1999). Alternatively, the one other report describing the use of SPECT in eclampsia demonstrated perfusion deficits in the watershed areas in women treated with magnesium sulfate. When SPECT was repeated a week later there was complete recovery of cerebral perfusion. These two seemingly conflicting reports show again the difficulty in interpreting the cerebrovascular abnormalities in preeclampsia.
Proton magnetic resonance spectroscopy (MRS) is a non-invasive method to investigate cerebral metabolism, in specific, the intracellular metabolite diffusion. Characteristic changes in the distribution of these compounds are detected in conditions where there is known cerebral ischemia or infarction such as stroke and carotid artery stenosis (Gillard 1996, Rutherford 2003). The main compounds detected are N-acetyl-aspartate (NAA), choline and lactate. First, the reduction in oxygen supply to cells causes the production of energy by anaerobic mechanisms leading to the accumulation of lactate. Reduced perfusion of tissues leads to disturbances in cellular metabolism that ultimately results in cell death. A decrease in NAA indicates neuronal loss.

In normal pregnancy, choline decreases with an ensuing increase in the NAA/choline ratio (Rutherford 2003). The lower level of choline in pregnancy may be a reflection of reduced stores throughout the body because of demands made by the fetus. Only 2 studies thus far have reported spectroscopy in pregnancy-related hypertension (Rutherford 2003, Sengar 1997). They contribute unique and important information regarding the pathogenesis of the central nervous system. Preeclampsia is associated with a lower NAA/choline ratio compared with healthy pregnancy due to increased choline (Rutherford 2003, Sengar 1997). This occurs particularly in edematous areas of the brain where T2 hyperintensity is apparent. The findings of higher choline with equivalent NAA in preeclampsia is thought to reflect relative cerebral ischemia without infarction. Absence of a lactate peak implies there is sufficient circulation to the cells within the brain to provide adequate oxygen and remove the products of anaerobic metabolism. In this situation ischemia is not severe enough to cause loss of neurons or build-up of lactate but is enough to cause membrane degradation and release of choline-containing compounds. The findings in women with preeclampsia are similar to those outside pregnancy. The authors suggest that a normal proces of adaptation has not occurred in women who develop preeclampsia or alternatively, these spectroscopic findings reflect cerebral ischemia (Rutherford 2003). One eclamptic patient studied with spectroscopy demonstrated a significant lactate peak (Sengar 1997). The presence of lactate as well as persistent low NAA even after complete reversibility of imaging abnormalities suggested the presence of infarction. On later follow-up there was a marked decline in NAA, which
correlated well with the development of cerebral atrophy resulting from gross neuronal damage.

Using near-infrared spectroscopy (NIRS) additional evidence is provided of altered cerebral hemodynamics in women with preeclampsia. Near-infrared spectroscopy (NIRS) is an optical technique that allows assessment of changes in tissue oxygenation and cerebral blood volume in realtime. Using this technique in women with several stages of hypertension, women with severe preeclampsia showed an increase in cerebral blood flow with posture changes (Chipchase 2003).

Conclusion

Various neuroimaging techniques discussed in this chapter have been utilized to evaluate the cerebrovascular hemodynamic condition in healthy pregnancy as well as in preeclampsia. To some degree such neuroimaging techniques have enhanced our knowledge of the pathogenic mechanisms underlying the cerebrovascular manifestations of 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.
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