Magnetic resonance imaging and cerebrovascular hemodynamics in (pre)-eclampsia

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Contents

Abbreviations

ADC	Apparent Diffusion Coefficient
CBF	Cerebral Blood Flow
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DWI	Diffusion Weighted Imaging
EDHF	Endothelium-Derived Hyperpolarizing Factor
EDRF	Endothelium-Derived Relaxing Factor
FLAIR	Fluid Attenuated Inverse Recovery
FOV	Field of View
HELLP	Hemolysis, Elevated Liver Enzymes Low Platelets
HTE	Hypertensive Encephalopathy
MAP	Mean Arterial Pressure
$MgSO_4$	Magnesium Sulfate
MCA	Middle Cerebral Artery
MIP	Maximum Intensity Projection
MMP	Matrix Metallo-Proteinase
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-Acetyl-Aspartate
NIRS	Near InfraRed Spectroscopy
NMR	Nuclear Magnetic Resonance
NO	Nitric Oxide
NSA	Number of Signals Averaged
PCA	Posterior Cerebral Artery
PRES	Posterior Reversible Encephalopathy Syndrome
SPECT	Single Photon Emission Computed Tomography
TIA	Transient Ischemic Attack
TCD	TransCranial Doppler
TE	Echo Time
TOF	Time of Flight
TR	Repetition Time

Aim of thesis

The aim of this thesis is to answer the following questions pertaining to the cerebrovascular disturbances in (pre)-eclampsia:

1. What are the neuroimaging features obtained with modern Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) techniques ?

2. Does human pregnancy elicit blood flow changes in large cerebral arteries and to what degree ?

3. What happens to cerebral blood flow in preeclamptic and normotensive women in the third trimester as compared to the non-pregnant state when employing velocity-encoded phase contrast magnetic resonance imaging techniques ?

4. What are the neuroimaging findings of eclampsia-related cerebral edema utilizing diffusion-weighted magnetic resonance imaging ?

5. What is the effect of a 6 gram intravenous loading dose of magnesium sulfate on maternal cerebral blood flow in women with severe preeclampsia ?

Outline of the thesis

The studies described in this thesis were performed at Parkland Memorial Hospital, the main teaching hospital of The University of Texas Southwestern Medical School in Dallas, Texas, USA. The protocols for these studies were approved by the University of Texas Southwestern Medical School Investigational Review Board for human investigation. All women participating in the cerebral blood flow studies gave informed consent. All participants had singleton gestations, confirmed gestational age, either by menstrual dates or by first or second trimester ultrasound. None had fetal anomalies, preterm labor or underlying disease such as chronic hypertension, epilepsy or diabetes mellitus. In addition, none had evidence of any chronic condition that may have affected cerebral blood flow. All control patients were followed until six weeks postpartum to ensure that they had experienced an uncomplicated pregnancy, delivery and puerperium.

Chapter 1

Recent development in neuroradiological imaging and hemodynamic cerebral assessment, in particular, Doppler ultrasound and MRI, have improved our understanding of the cerebrovascular condition in pregnancy and preeclampsia. Therefore, MRI techniques will be discussed as they pertain to basic technology as well as diffusion MR imaging to assess the origin of cerebral edema. Subsequently, velocity-encoded phase contrast MRI to quantify cerebral blood flow will be reviewed. Lastly, alternative techniques that have been used to study cerebrovascular changes in preeclampsia will be briefly mentioned as well.

Chapter 2

This chapter reviews the recent neuroimaging features in (pre)-eclampsia obtained with modern CT and MRI techniques such as diffusion-weighted imaging and velocity-encoded phase-contrast MRI. Based on this information, considerations regarding the etiopathogenesis of the cerebrovascular disturbances in preeclampsia as well as clinical practice when confronted with the hypertensive gravida will be discussed.

Chapter 3

The purpose of this study was to evaluate possible blood flow changes in the large cerebral arteries during normal pregnancy. Ten healthy pregnant volunteers underwent velocity-encoded phase contrast MRI at three time intervals during pregnancy 14-16, 28-32, and 36-38 weeks' gestation, and at six to eight weeks postpartum. The nonpregnant values were used for comparison.

Chapter 4

This study compares third trimester and nonpregnant cerebral blood flow in preeclamptic and normotensive women. Nine normotensive healthy pregnant women and twelve untreated women with preeclampsia underwent velocity-encoded phase contrast MRI of the bilateral middle and posterior cerebral arteries in the third trimester and at six to eight weeks after delivery. In addition, FLAIR imaging was employed as well to detect the possible presence of cerebral edema.

Chapter 5

This study further characterizes the neuroimaging findings of eclampsia-related cerebral edema as it describes the cranial MR imaging studies of twenty-seven nulliparous eclamptic women. These women were studied within thirty-six hours of the last convulsion to include magnetic resonance FLAIR, diffusion–weighted MRI and apparent diffusion coefficient mapping. Those with findings suggestive of ischemia-related cytotoxic edema underwent neuroimaging again six weeks postpartum.

Chapter 6

This study was designed to determine 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.

Chapter 7

There remain many unanswered questions regarding the etiopathogenesis of the cerebral manifestations of (pre)-eclampsia. 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. This chapter discusses why eclampsia appears comparable to this particular syndrome, also called hypertensive encephalopathy. This chapter also summarizes the conclusions of this thesis as well as directions for future research in the field of cerebrovascular adaptations to pregnancy, and pregnancy-related hypertensive disorders in particular.

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 ma, 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). Usint 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 polymerizaton 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 N^{w}-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, vitamine 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 usefullness (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, saggital 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 equillibrium 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 4^{th} 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 velocites 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 complicance can increase impedance indices without changes in vascular resistance.

Multiple studies, both longitudinally as well as cross-sectionally in healthy pregnancy have demonstrate 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_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.

Spectroscopy

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 reversiblity 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 cerebal 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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Chapter 2.

Neuroradiological imaging in (pre)-eclampsia: a review

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Submitted

Abstract

Objective

To describe the neuroimaging findings in (pre)-eclampsia; to relate these findings to possible mechanisms in the pathogenesis of the cerebrovascular disturbances.

Study design

Pubmed was searched from 1980 – 2004 using the key words “preeclampsia, eclampsia, computed tomography (CT), magnetic resonance imaging (MRI). All articles were cross-referenced.

Results

CT and MRI primarily demonstrate transient lesions consistent with vasogenic edema in the (sub)-cortical regions of the parieto-occipital lobes. With diffusion-weighted MRI evidence for cytotoxic edema is now also found. Up to a fourth of, seemingly asymptomatic eclamptic women demonstrate permanent infarctions.

Conclusion

Eclampsia may represent the end stage of at least 2 different pathophysiological pathways; vasospasm versus increased cerebral blood flow. MR diffusion sequences may characterise the cerebral edema. Reversible Posterior Leucoencephalopathy Syndrome (RPLS) may serve as a model for eclampsia. The two conditions have many pathologic, radiologic, and clinical features in common. However, eclampsia should not be conceptualized as a solitary event but as a disorder with possibly lifelong sequelae

Eclampsia: Incidence, mortality and autopsy

Eclampsia is defined as the occurrence of tonic-clonic convulsions in pregnant or recently postpartum women with preeclampsia. Other dramatic neurological presentations, albeit uncommon, include blindness, altered state of consciousness and coma. Recent estimates of the incidence of eclampsia in the United States range from 0.6 to 3/1000 live births [Mattar 2000, Abi-said 1995, Saftlas 1990.] Eclampsia is considerend one of the most frequent causes of maternal death; approximately 50,000- 65,000 deaths occur per year worldwide [Lancet 1995 collaborative, confidential enquiries.] In the USA, the United Kingdom, and other developed countries such as Sweden, (pre)-eclampsia is the 2nd leading cause of maternal mortality [Kaunitz 1985, Rochat 1988, Moller, Douglas.] In The Netherlands (pre)-eclampsia is the leading cause of maternal death; 35 % of women classified as direct maternal death died due to complications of (pre)-eclampsia [Schuitemaker 1998.] In the USA 23 % of maternal deaths recorded in 1997 were related to pregnancy hypertension. [Williams Obstetrics] The acute cerebral complications of (pre)-eclampsia such as intracranial hemorrhage or massive cerebral edema account for at least 75 % of such fatalities, particularly in the presence of HELLP syndrome [Llopez Llera 1982, Okanloma 2000, Isler 1990.]Less well known is that (pre)-eclampsia also accounts for nearly 50 % of, mostly clinically reversible, pregnancy-related ischemic strokes [Sharshar 1995, Kittner 1996, Wiebers 1985.] Improvement in antenatal and intensive care has reduced the incidence of and death attributable to eclampsia in western countries over the past decade. Modern maternal mortality rates of < 0.5 % are now reported [Sibai 1990, Pritchard 1984.]

Pathogenesis

Information whether pregnancy elicits physiologic adaptations in cerebral blood flow is virtually non-existent compared with our knowledge of the alterations in other vascular beds during gestation. This is partly due to technical difficulties associated with in vivo studies of blood flow in the human brain. Obviously, there are ethical and logistic problems using angiography or other techniques involving radioactive tracers during pregnancy. Transcranial Doppler velocimetry of the middle cerebral artery has been employed most widely to study cerebral blood flow velocity Belfort 1999, 1999, Williams 1993, 1994. The interpretation of these Doppler data is limited since cerebral blood flow velocity measurements can not be extrapolated into flow volume measurements without making several assumptions.

There remain many unanswered questions regarding the pathogenesis of the cerebral manifestations of eclampsia. Human experimental data regarding the cerebral responses to hypertensive disease in pregnancy are scant. In addition, there is obvious difficulty in relating the histopathologic data with the hemodynamic information. By necessity, the central nervous system histopathology of eclampsia is based on autopsy specimens from women who died of the condition, while the hemodynamic data are taken from surviving patients with (pre)-eclampsia. Over the years, two theories have been proposed to explain the cerebral abnormalities associated with eclampsia. First, cerebral overregulation with vasospasm is thought to occur in response to acute severe hypertension Ito 1995, Trommer 1988**.** Alternatively, “forced” vasodilation is thought to occur in response to a breakthrough of cerebral autoregulation Strandgaard 1984, Hauser 1988, Schwartz 2000, Paulsen 2002. These two distinct theories will be discussed in more detail in the paragraph concerning cerebral autoregulation.

Prior to the 1980’s only electroencephalography (EEG) was available in the armamentarium to evaluate the cerebral response in the eclamptic patient. The EEG is acutely abnormal and shows diffuse or focal slowing with delta or beta waves Moodley 1993 Sibai 1984 and gradually returns to normal 6-8 weeks postpartum. The patterns described are not pathognomonic of eclampsia as similar patterns are seen in a variety of conditions Royburt 1991. Several recently developed neuroradiological imaging techniques have greatly improved our understanding of the correlation between the neurological symptoms and neuroanatomic pathological changes characteristic of (pre)-eclampsia.

Autopsy findings

The few autopsy series that exist describe gross intracerebral hemorrhage occurring in up to 60 % of patients [Melrose 1984, Sheehan 1973, Richard 1988, Govan 1961]. The incidence of cerebral hemorrhage in nonfatal eclampsia is unknown. The other principal macroscopic postmortem lesions consist of cortical petechial hemorrhages [Sheehan 1973]. Histologically, these lesions are composed of numerous small hemorrhages, 0.3-1.0 mm in diameter, arranged in streaks of 2-4 cm running radially in the cortex. They may appear anywhere on the gyral surface and are most common in the occipital lobes and least common in the temporal lobes. Many occur in the border zones between major cerebral arterial supplies. Other frequently found macroscopic major lesions described include multiple nonhemorrhagic areas of “softening” throughout the brain, small hemorrhagic areas in the white matter, single large hemorrhage in the white matter, and hemorrhage in the basal ganglia or pons, often with rupture into the ventricles. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular hemorrhages. Interestingly, in several cases numerous small areas of the cortex are infarcted [Sheehan 1973]. These infarcts vary from about 0.3-1.0 mm in diameter and are sometimes confluent. Small hemorrhages are commonly present inside the infarcts and a number of the precapillaries show stasis and thrombosis. These histopathologic findings correspond to several of the neuroimaging findings as discussed in this review.

The purpose of this systematic review is to describe the neuroimaging findings of women suffering (pre)-eclampsia as they have emerged over the last 2 decades with the use of CT and MRI scanning. Based on this literature, current considerations regarding the etiopathogenesis of cerebrovascular disturbances in (pre)-eclampsia as well as implications for clinical practice will be presented.

Search and study selection

Prior to 1980 no reports on cerebral imaging in (pre)-eclampsia were available. PUBMED/MEDLINE was searched from 1980 through 2004 and all articles cross-referenced. The following key words were employed: preeclampsia, eclampsia, computed tomography (CT) and magnetic resonance imaging (MRI). Single case reports are not necessarily quoted unless revealing important new or unique information.

Results

Neuroimaging of cerebral edema

Computed tomography

In the early 1980's the first single case reports describing the appearance of cerebral edema in eclampsia using computed tomography (CT) were published Benedetti 1980, Baker 1982, Grimes 1980, Beck 1981, gaitz 1982, Waldron 1985, Colosimo 1985, Naheedy 1985.

Localised hypodense lesions at the gray-white matter junction are typically found primarily in the parieto-ocipital lobes (Figure 5). Less commonly, such lesions may be found in the frontal and inferior temporal lobes [Brown 1988]. Deep white matter abnormalities have also been reported along with hypodense lesions of the basal ganglia and thalamus [kirby 1984, Kokcu 1993]. Several case series showing evidence of reversible cerebral edema have since been added to the literature [Koyama 1997, Sarma 2003, Moodley 1993]. Surprisingly, some CT scans in eclamptic women did not demonstrate any lesions [Sibai 1990]. This may represent true absence of such lesions or limitations of the contemporaneous technique in detecting more subtle lesions. Generally, the hypodense lesions are completely reversible but not all reports document the availability of follow up scans. Importantly, cerebral infarcts have been demonstrated with CT in eclampsia [Moodley 1993, Gaitz 1982]. In the absence of eclamptic seizures or other serious neurological symptomatology CT and MRI findings are not abnormal in women with severe preeclampsia. In addition, the hypodense lesions typically found

in eclampsia are not usually seen in normotensive pregnancies nor in pregnant women with chronic hypertension [Milliez 1990].

Some reports deserve special mention. Widespread diffuse cerebral edema instead of the more typical low density areas is described in women with persistent neurologic symptoms such as lethargy, confusion and blindness [Richards 1986, Cunningham 2000]. In these cases mass effect was present as demonstrated by a marked compression or even obliteration of the cerebral ventricles (Figure 6). Such women may have signs of impending life-threatening transtentorial herniation. Postmortem investigation reveals fibrinoid arterial wall necrosis, perivascular microinfarcts and brain edema as well as widespread hypoxic ischemic neuronal damage [Richards 1988].

The development of frank hemorrhage into previous areas of ischemic cerebral infarction in a woman with eclampsia is elegantly described and depicted by Salerni et al [1988].This sequence of events is responsible for a well-established complication in patients with occlusive atherosclerotic cerebrovascular disease [Drislane 1997]. Hypertension and coagulopathy are known to increase the risk of hemorrhagic transformation into previously ischemic areas of the brain in atherosclerotic disease. These comorbid circumstances may also proof to be important in the progression to cerebral hemorrhage in (pre)-eclampsia. The sequential demonstration of CT images in this report raises important issues regarding both the pathogenesis of (pre)-eclampsia related intracranial hemorrhage and its prevention.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is well known for its far more superior soft tissue contrast and multiplanar resolution compared to CT. This technique is therefore extremely effective for the diagnosis of hemorrhage as well as ischemia or edema. Since late 1980's to early 1990's many case reports [Schwaighofer 1989, Raroque 1990, Koyama 1997, Malow 1990, Marano 2003, Vandeplas 1989, Crawford 1987, Frederiksson 1989, Veltkamp 2000] and case series [Schwarts 2000, Morriss 1997, Sanders 1991] describe hyperintense reversible lesions with T2 MR imaging in nearly all women with eclampsia (Figure 7). Where CT is often reported normal in case of cerebral edema, MRI demonstrates transient T2 lesions in the (sub) cortical regions of the parieto-occipital lobes [Dahmus]. Occasional involvement of basal ganglia and/or brainstem is also reported (Figure 8) [Zeeman 2004]. Women with

atypical late eclampsia 6-13 days postpartum have shown low-density areas on CT and positive T2 MRI as well [Raps 1993 and Bartynski 2003] . Women with preeclampsia in the absence of eclamptic convulsions typically do not exhibit such lesions on MRI unless they have neurological symptoms such as visual disturbances or vertigo [Schwartz 2000, Morris 1997, Digre 1993]. Morriss et al found subtle changes on T2 MRI in only 2/10 severely preeclamptic women based on increased signal intensity, compared to markedly abnormal findings of increased T2 signal intensity in a number of locations in all women with eclampsia. The 2 women with preeclampsia had several neurologic symptoms such as headache, vertigo or visual disturbances. These hyperintense lesions are typically thought to resolve without longterm sequelae. Few small case series describe persistent hyperintense T2 lesions that may actually represent permanent brain lesions consistent with infarctions. [Sharshar 1995, Rapps 1993, Sanders 1991, Servillo 2003]

Diffusion Weighted Magnetic Resonance Imaging and Apparent Diffusion Coefficient mapping (DWI/ADC)

Two distinctly different types of cerebal edema, vasogenic and cytotoxic edema, can be distinguished by using certain neuroimaging techniques. Roughly, vasogenic edema is associated with increased hydrostatic pressure and ensuing capillary leak while cytotoxic edema is associated with cell death. Using conventional CT and MRI techniques it is impossible to differentiate between these two forms of cerebral edema. With a series of MR acquisitions including Diffusion-Weighted Imaging sequences (DWI) and Apparent Diffusion Coefficient mapping (ADC) it is now possible to further characterize the hyperintense lesions seen on T2 MR imaging in eclamptic women (Figures 9 -11). The DWI technique is based on the quantification of the diffusion of free water, which is decreased in ischemic brain tissue. It is possible to identify ischemic brain regions within minutes to hours after onset of neurologic symptoms as an area of high signal intensity compared with the signal from normal brain [Burdette 1999, Li 1998, Chien 1992, Warach 1995]. With an ischemic event in evolution a shift of water from the extracellular to the intracellular space results in restricted diffusion and therefore reduced ADC values. This is thought to result from decreased Na^+ K^+- ATP-ase activity in glial cell membranes and consequent

decrease in water molecule transport with ensuing cell death. Such areas appear hyperintense on DWI and represent cytotoxic edema [Burdette 1999]. Quantitatively, the regional ADC values provide a non-invasive tool for monitoring the time evolution and spatial expansion of ischemic lesions. A combination of normal DWI with high T2 signal lesions and increased ADC represents reversible vasogenic edema. Several case reports and case series of eclampsia describe reversible lesions on T2 MR imaging. Studies using additional diffusion-weighted imaging sequences showed that the origin of brain edema in eclampsia is primarily vasogenic, but less commonly, may be associated with ischemic/cytotoxic changes [Friese 2000, Chakravarty 2002]. In such cases DWI hyperintense lesions occur superimposed on the pattern of vasogenic edema with decreased ADC. Of the fifteen single case reports describing neuroimaging features in eclamptic women using these new imaging techniques two women appeared to have infarcts [Schwarts 2000, Koch 2001, Kanki 1999, Jurgensen 2001, Keswani 2000, Schaefer 1997, Schwarz 1998, Mukherjee 2001, Ohno 1999, Chakravarty 2002, Engelter 2000, Friese 2000.] Following these case reports very recently two small [Watanambe 2002, Shah 1999] and two larger case series [Louiero 2003, Zeeman 2004] were reported also taking advantage of these MRI techniques for the evaluation of women with eclampsia. It appears that 20-25 % of women with eclampsia demonstrate lesions consistent with cerebral infarction [Loueiro 2003, Zeeman 2004]. Such lesions were still present on follow up imaging 6-8 weeks later and seem to correspond with the classic neuropathologic data demonstrating evidence of cerebral infarction [Sheehan 1973, Richards 1988]. It has to be mentioned that all these women were normotensive as well as asymptomatic at time of the follow up imaging studies. Unfortuately, detailed neurocognitive studies were not performed in these women to document possible immediate clinical relevance. Nevertheless, it is now well known that subclinical infarcts and white matter lesions in general are related to an increased risk of adverse sequelae including clinical stroke events, physical limitations and cognitive impairment including dementia [Longstreth 1996, Bernick 2001, Vermeer 2003]

Angiography

As discussed earlier many believe that vasospasm is the primary event leading to eclampsia [Trommer 1988, lewis 1988, Will 1987.] This presumption is based on the angiographic appearance of diffuse or multifocal segmental narrowings or vasospasm of the cerebral vasculature. Abnormal findings consistent with vasospasm of large and medium-sized cerebral arteries in the absence of underlying intracranial hermorrhage have been found up to two weeks postpartum in women with severe preeclampsia and eclampsia [Kanayama 1993, Ito 1995, matsuda 1995, Sengar 1997, Rape 1993, Trommer 1988, Call 1988]. Several single case reports employing conventional angiography or magnetic resonance angiography (MRA) [Kanayama 1993, Ito 1995, Hashimoto 1997] and a few case series demonstrate such phenomenon whereas just as many others refute this [Morris 1997, Rutherford 2003, Kobayashi 2001, Matsuda 1995]. Recent experimental data suggest that the appearance of vasospasm on angiography is consistent with a so-called sausage string pattern linked to the development of vascular damage [Jacobsen 2002]. Although it has been known for decades that arteries and arterioles can assume a shape characterised by regular symmetric and alternating areas of constriction and dilatation, the mechanisms underlying this phenomenon have remained an enigma.

Neuroimaging of hemorrhagic complications

In some women with eclampsia sudden death occurs synchronously with a convulsion or follows shortly thereafter, and is a result of massive cerebral hemorrhage. Non-lethal intracranial hemorrhage is also frequently found in (pre)-eclamptic women who undergo neuroimaging due to an abnormality on neurological examination. Cerebral hemorrhage is more common in older women with underlying chronic hypertension [Williams 22nd edition]. The cause of such hemorrhages is known to be due to longstanding hypertension-induced lipohyalinosis, which damages small or medium sized cerebral arteries. The striatocapsular area, thalamus, cerebellum and brain stem are the sites most frequently affected in such hypertensive intracerebral hemorrhage [Imaizumi 2004]. Alternatively, as described by Salerni et al [1988] cerebral infarction may transform into a hemorrhagic infarction. Such intracerebral hemorrhage may be more common in young nulliparae who present with HELLP syndrome and eclampsia although this is speculative. Only rarely, is intracerebral hemorrhage in women with (pre)-eclampsia due to a ruptured aneurysm or arteriovenous malformation [Witlin 1997.]

Occasionally, subarachnoid hemorrhage is reported in (pre) eclampsia [Shah 2003, Gregory 2003, Drislane 1997.] In such cases a small amount of blood is seen over the convexity of the frontal/parietal lobes extending into the sylvian fissure or interhemispheric tissue. Conventional angiography rules out ruptured arterial-venous malformation or intracranial aneurysm, or cortical venous sinus thrombosis. Subarachnoid hemorrhage in (pre)-eclampsia is hypothesized to be the result of rupture of cortical petechiae over the surface of the brain or rupture of small pial veins. This type of subarachnoid hemorrhage seems to carry a benign prognosis since none of the patients described developed permanent neurologic deficits on follow-up exam [Shah 2003, Gregory 2003, Drislane 1997.]

Two additional unique case reports deserve mention in this review. Giannina describes a spontaneous antepartum subdural hematoma associated with preeclampsia /HELLP in conjunction with trombopenia. Uncal herniation resulted in the death of the patient [Giannina 1997.] Biller 1995 describes an eclamptic patient with a right basal ganglia hematoma that subsequently transformed into an abcess. It is hypothesized that the infection occurred through bacterial seeding from an infected episiotomy.

Neuroimaging in the presence of visual disturbances

Visual symptoms may occur in 40 % of preeclamptic women and on rare occasions may be the initial symptom. They include scotomota, amaurosis, blurred vision, diplopia, chromatopsia or homonymous hemianopsia [Weiner 1987.] In the past, blindness was usually attributed to retinal abnormalities to include edema, vascular changes such as retinal arteriolar vasospasm or thrombosis of the central retinal artery or retinal detachment. Now, with the introduction of newer neuroimaging modalities such as MRI, focal cerebral edema including bilateral edema of the lateral geniculate nuclei may be seen [Moseman 2002]. Therefore, the term “cortical blindness” was introduced. Cortical blindness is characterised by intact pupillary light reflexes, intact ocular movements and normal opthalmologic findings thus excluding a peripheral cause of blindness.

Neuroimaging findings in cases where visual distrubances dominate the clinical picture, have ranged from normal to widespread low-density areas on CT [Beck 1981, Beeson 1982, Ozkan 2001, Apollon 2000, Waldron 1985, Schimp 2001, Kesler 1998, Borromeo 2000, Herzog 1990, Waldron 1985, Lau 1987]. The absence of lesions may be due to the limited resolution capacity of CT. Follow up imaging generally demonstrates complete resolution of lesions on CT [Iimaizuzmi 1995, Manfredi 1997.] The majority of (pre)-eclamptic women with cortical blindness recover vision over a period varying from two hours to twenty-one days [Duncan 1989, Cunningham 1995.] Although there are reported cases of persistent deficit [Moseman 2002, Lara, Park 2000,] clinical recovery typically precedes normalization of neuro-imaging findings.

In eclamptic women transient blindness is estimated to occur in about 1-15 % [Cunningam 1995, Torres 1995.] The largest series was reported by Cunningham who describes fifteen such women over a fourteen-year period. These women typically demonstrate low-density areas on CT and T2 hyperintense lesions on MRI. Lesions are seen particularly in the parieto-occipital area and supplied by the posterior circulation, and are reversible on follow up imaging [Do 2002, Chambers 2004, Apollon 2000, Torres 1995, Duncan 1989, Herzog 1990.] The presence of transiently increased velocity using transcranial Doppler ultrasound [Torres 1995] and the presence of vasogenic edema in the absence of restricted diffusion (i.e. no evidence of ischemic lesions) using diffusion MRI seems to confirm this finding [Jurgensen 2001, Chambers 2004].

So far, only three women have been described in the literature demonstrating permanent blindness. Two of them had a combination of both abnormal retinal findings consistent with Purtschers retinopathy and MR evidence of brain infarcts located in the lateral geniculate nuclei [Blodi 1990, Moseman 2002].The third patient with persistent blindness did not undergo MR imaging and therefore no conclusions can be drawn [Lara 2002.] Two additional case reports deserve mention. Delefosse describes a case of transient cortical blindness in a woman who was 26 days postpartum. The authors concluded that retained placental fragments may be associated [Delefosse 2003].

Finsterer describes a preeclamptic patient who suffered transient cortical blindness after nitroglycerin administration. MR imaging with diffusion sequences demonstrated a typical picture of vasogenic edema. The authors conclude that nitroglycerin may aggravate the development of vasogenic edema secondary to enhancement of cerebrovascular vasodilation and may result in cortical blindness by this mechanism.

Cerebral autoregulation

Cerebral autoregulation is the process by which cererbal blood flow remains constant in the face of alterations in cerebral perfusion pressure [Strandgaard 1984, Paulson 1990.] Cerebral autoregulatory mechanisms protect the brain from acute hemodynamic pertubations. Cerebral blood flow in a nonpregnant healthy individual is generally maintained constant over a mean arterial pressure range of 60-150 mm Hg [Paulson 1990]. Whether pregnancy evokes an adaptation of this range is unknown, although alterations due to chronic hyperventilation are proposed [van Hook 1999]. Likewise, it is tempting to hypothesize a shift of this autoregulatory range in the presence of pregnancy complications such as preeclampsia. Again, whether this occurs is unknown but a substantial disturbance of certain features pertaining to cerebral autoregulation in eclampsia is reported [Oehm 2003.]

Cerebral autoregulatory mechanisms consist of both myogenic and neurogenic components, such as the sympathetic tone. Counteraction of increased systemic blood pressure is achieved primarily by varying arteriolar resistance through

changing the vessel diameter [Paulson 1990]. The area supplied by the posterior circulation is most vulnerable to a possible failure of autoregulatory mechanisms since this area has less sympathetic innervation and may have the least ability for neurogenic response to increased blood pressure [Lassen 1973]. The cerebral white matter is composed of myelinated fiber tracts in a cellular matrix of glial cells, arterioles and capillaries. This composition causes susceptibility to the accumulation of fluid, vasogenic edema, in the extracellular spaces [Beausan 1981, Schwartz 1998, Port 1998].

The clinical, pathological, and neuroimaging findings in eclampsia have led to two major theories centered around the phenomenon of cerebral autoregulation. According to the first, extreme vasospasm of the cerebral vasculature occurs as a response to acute hypertension [Ito 1995, Trommer 1988]. Subsequently, cerebral blood flow is thought to decrease, and when extreme, is hypothesized to result in ischemia, cytotoxic edema and, eventually, tissue infarction. According to the alternate concept, sudden elevations in systemic blood pressure may exceed the cerebrovascular autoregulatory capacity. When autoregulation fails, regions of passive vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level disruption of the end-capillary pressure occurs with subsequent increase in hydrostatic pressure. This may result in hyperperfusion and extravasation of plasma and red cells through opening of the endothelial tight junctions, which may lead to the accumulation of vasogenic edema [Schwartz 2000, Hauser 1988, Strandgaard 1984, Paulsen 2002]. This latter theory has gained much attention recently, also in the non-obstetric literature. This phenomenon is coined reversible posterior leucoencephalopathy syndrome (RPLS) and includes the, more familiar, clinical diagnosis of hypertensive encephalopathy [Hackett 1998].

The next paragraph elaborates on the similarity of the cerebrovascular mechanisms in eclampsia with RPLS. In adddition, implications of this theory for the clinical management of hypertensive disorders of pregnancy are explored.

Is eclampsia a form of reversible posterior leuco-encephalopathy syndrome (RPLS) ?

The role of vasospasm as the primary mechanism for convulsions in women with preeclampsia is challenged by the neuroimaging data presented in this review. Impaired cerebral autoregulation is now increasingly thought to be the major determinant for the development of eclamptic encephalopathy. Reversible Posterior Leucoencephalopathy Syndrome (RPLS) is hypothesized to be the primary injury based on its clinical, pathological, as well as neuroimaging features [Hinchey 1996 , Schwartz 1998, Pavlakis 1999, Williams 1996, Easton 1998, Hatashita 1986, Kontos 1981]. In non-pregnant patients RPLS may occur after a subacute elevation of blood pressure. Areas of cerebrovascular vasodilation and vasoconstriction may both coexist in the acute phase of hypertension [Edvinsson 2002]. The clinical presentation is variable and may include headaches, seizures, visual changes, altered mental status, and occasionally focal neurologic signs. Endothelial cell dysfunction is thought to play a prominent role in the etiopathogenesis of RPLS. Endothelial injury leads to altered regulation of the vascular response to systemic vasoactive metabolites such as angiotensin-II, as well as to intrinsic release of endothelial vasoactive substances, resulting in blood vessel hyperactivity and labile blood pressure [Roberts 1989, Taylor in Chesley 1999, Harder 1987, Redman 1999]. Endothelial cell dysfunction resulting in increased barrier permeability is also thought to play a major role in preeclampsia [Roberts 1989, Taylor 1999, Redman 1999]. In the transplant population RPLS is a well-known complication of immunosuppressive therapy [Schwarz 1995], possibly based on the same mechanisms of endothelial cell dysfunction. It may also be seen in the setting of uremia, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) [Kinshita 2003]. RPLS is reported with the use of chemotherapeutic agents such as cisplatin, interferon A, intrathecally administered methotrexate as well as in patients with acute intermittent porphyria and cryoglobinuria [Covarrubioas 2002, Port 1998, Schwarz 1998].

Why do some women with a relatively mild hypertension develop eclamptic convulsions ? It is tempting to hypothesize that the upper limit of cerebral autoregulation is reduced in women (pre)-eclampsia but evidence for this is lacking. From clinical observation it seems that failure of cerebrovascular autoregulatory mechanisms may occur in response to either a rapid and/or relatively large blood pressure increase. Subsequently, forced overdistension of the cerebral vasculature

poses risk for vessel damage and barotrauma. This is illustrated in women with preeclampsia by finding increased cerebral blood flow using velocity-encoded phase contrast MRI [Zeeman 2004] and increased cerebral perfusion pressure using transcranial Doppler ultrasound [Riskin 1999, Williams 1998]

Implications for practice

The rational approach to Reversible Posterior Leucoencephalopathy Syndrome in pregnancy

The effect of normal pregnancy, let alone, preeclampsia, on the upper limit of mean arterial pressure at which autoregulation operates is unknown. Almost a fifth of eclamptic women reportedly have maximum systolic blood pressures of < 140 mmHg prior to the event [Sibai 1990, Mattar 2000.] Although the risk of convulsions seems certainly greater in clinically severe compared to mild preeclampsia, reliance on the level of blood pressure for grading severity of disease can be disastrous. This was recently shown by Martin et al [2005] who scrutinized the peripartum course of 28 preeclamptic women who experienced a hemorrhagic stroke. Severe diastolic hypertension (>110 mmHg) did not necessarily develop prior to the event. Indeed, the great majority of the patients in this case series never exhibited a single or sustained diastolic blood pressure of 105-110 mmHg.

Furthermore, blood pressure treatment alone does not necessarily seem to prevent the development of RPLS nor hemorrhagic stroke. Autoregulation is abnormal in these patients and, as said, prediction of the degree of dysfunction and in whom it will occur is difficult. In general, blood pressure needs to be reduced to a safe range to avoid loss of cerebral autoregulation. As discussed in the prior paragraph, likely because of endothelial dysfunction, preeclampsia is capable of regionally affecting vascular smooth muscle function. Alterations in the cerebral circulation in (pre)-eclamptic women may occur despite minimal elevation in blood pressure. Eclamptic women with such borderline hypertension are often young primigravidas whose blood pressures have risen markedly from low levels. The

critical threshold could be related to the patients customary blood pressure prior the development of hypertension. Furthermore, the relative rapidity of changes may be of primary importance although this is difficult to study.

Accurate evidence based recommendations for the use of antihypertensive treatment in women with severe (pre)-eclampsia do not exist, however. The final recommendation of the NICHD Working Group Report, and as such endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP), is to treat acute severe hypertension in (pre)-eclampsia when systolic blood pressure is > 160 mmHg and/or diastolic blood pressure is sustained > 105 mmHg [NICHD 2000].

Most seizures occur during the intrapartum and postpartum periods. None of the clinical signs and symptoms considered to be prognostic of seizures are absolutely reliable. [Sibai 1981] Symptoms may occur before or after the onset of convulsions, and they include persistent occipital or frontal headaches, blurred vision, photophobia, epigastric or right upper quadrant pain, and altered mental status. Patients will have at least one of these symptoms before the onset of eclamptic convulsions in 60-75 % of the cases [Sibai 2005]. Headache may herald the loss of autoregulation and clinically this makes sense.

The lack of a full understanding of the etiology of eclamptic convulsions has mounted in considerable disagreement considering the best anticonvulsant for the prevention and control of such seizures. Without going into much detail, which is the focus of other excellent reviews [Sibai 2004, 2005, Katz 2004], the use of magnesium sulfate for the prevention and treatment of eclamptic seizures has been well supported despite the fact that we know very little of its mechanisms and actions [Magpie 2002, Witlin 1999,Sibai 2004]

Do all women with eclampsia need neuroimaging studies ?

One can question the indication for neuroimaging studies in eclampsia or when (pre)-eclampsia is complicated by transient blindness, especially if the clinical course is typical, with prompt response to therapy. Most reported cases of blindness in pregnancy have been secondary to cortical cerebral edema and thus are often labelled as cortical blindness. These women typically have normal fundoscopic examinations and lesions consistent with cerebral edema on MRI. Cortical blindness is almost always transient as are the neuroimaging findings associated with it.

Recurrent eclamptic seizures refractory to magnesium sulfate, however, may be associated with structural central nervous system abnormalities such as sinus thrombosis [Dunn 1986.] Whilst epilepsy and eclampsia will account for most peripartum seizures all cases where atypical signs exist require thorough neurological examination [Keay, Konstantinopoulos 2004.] Neuroimaging studies could generally be limited to those women who have additional focal neurological signs, prolonged coma, atypical convulsions and those who have a prolonged return to complete recovery following delivery. In such women hemorrhage or other serious abnormalities requiring specialised interventions must be promptly excluded. MRI is much more often contributory compared with CT in patiens with hypertensive disorders of pregnancy [Dahmus 1992, Manfredi 1997]. The use of MRI diffusion and ADC mapping allows an earlier and clearer differentiation of cytotoxic and vasogenic edema. Even though the clinical Consequences of making this distinction are still limited at time of this review, employing this type of imaging may have important prognostic implications for eclamptic women in the future [Zeeman 2004, Loureiro 2003.]

Conclusions

Eclampsia is almost exclusively a disorder of human pregnancy, the pathogenesis of which remains unknown. For ethical reasons experimental studies precisely evaluating the cerebrovascular condition are far and few between. Based on similarities both radiologically and clinically as well as pathologically, attention is directed towards Reversible Posterior Leucoencephalopathy Syndrome (RPLS) as a comparable model. Specialised MR findings sugggest a continuum of pathology that is proportionally associated with the severity of the clinical findings including hydrostatic edema. If severe enough, such edema may result in cellular ischemia and irreversible cell death [Tamaki 1984]. It is now demonstrated that up to one fourth of eclamptic women may have evidence of cerebral tissue loss 6 weeks postpartum. There are no reliable predictors no signs or symptoms to forecast the development of eclampsia in women with hypertensive disorders of pregnancy. Eclampsia is rarely associated with persistent, clinically recognizable, neurologic morbidity and epilepsy is not a recognized longterm complication [Sibai 1985.] However, intra-cerebral hemorrhage is a well-known cerebrovascular complications of eclampsia frequently leading to maternal death or major permanent disability. The proposed progression from ischemic to hemorrhagic infarction in eclamptic patients may have important therapeutic implications. In general, therapy should be directed toward lowering blood pressure so as to limit the further development of vasogenic edema and subsequent ischemia. Therapy should also include treatment with Magnesium sulfate, and maintaining adequate platelet levels to avoid hemorrhage.

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Chapter 3.

Maternal cerebral blood flow changes in pregnancy

Zeeman GG, Hatab MR, Twickler DM.
Am J Obstet Gynecol 2003;189:968-72

ABSTRACT

Objective

To determine blood flow changes in the large cerebral arteries during normal pregnancy.

Study Design

Ten healthy pregnant volunteers underwent velocity-encoded phase contrast magnetic resonance imaging at 4 time intervals, 14-16, 28-32, and 36-38 weeks´ gestation, and at 6-8 weeks postpartum. Analysis consisted of serial paired Student t-tests, with $p < 0.05$ considered significant

Results

Using postpartum values for comparison cerebral blood flow decreased by 14-16 weeks in the middle ($p < 0.001$) cerebral artery, but was not significantly changed in the posterior cerebral artery. Significant decreases occurred in both the middle ($p < 0.0001$) and posterior ($p = 0.002$) cerebral arteries in late pregnancy.

Conclusion

An approximately 20 % reduction in large artery cerebral blood flow occurs during normal pregnancy, secondary to changes in velocity while the area of these vessels remains unchanged. These findings may represent generalized vasodilatation of downstream resistance arterioles, assuming constant blood flow at the tissue level.

INTRODUCTION

Normal pregnancy induces a multitude of rather profound physiologic hemodynamic alterations. Among these are substantive increase in total blood volume, cardiac output, and uterine blood flow. Technical challenges are encountered when assessing cerebral blood flow in the human. Accurate methods have been either invasive or they require radioactive substances. The non-invasive transcranial Doppler technique introduced by Aaslid [1] is a method that is now widely used to assess the intracerebral circulation. It has been used extensively for neurosurgical patients for the early detection of cerebral vasospasm following subarachnoid hemorrhage. During the past decade, this technique has been increasingly used in obstetrics beginning with studies to estimate blood flow velocity in preeclampsia and eclampsia.[2-6]

Other than early studies of cerebral blood flow by McCall, [7] there are none that report use of invasive methods to assess cerebral blood flow. In the past decade, however, a number of researchers have reported pregnancy-induced changes from velocity measurements of the middle cerebral arteries utilizing transcranial Doppler. These have included both longitudinal [3,8] as well as cross-sectional studies.[9-11] In aggregate, these studies indicate that middle cerebral artery velocity decreases with advancing gestation and then returns to nonpregnant values in the puerperium. While these observations are compatible with physiological vasodilatation seen in other regional blood flow systems during pregnancy, the transcranial Doppler technique can be used only to estimate blood flow. Accurate assessment of absolute blood flow is dependent on vessel diameter, which cannot be determined with this method.

More recently, magnetic resonance imaging techniques have been developed that 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.[12-15] This method has excellent correlation with traditional invasive methods, such as cardiac catheterization and the Fick principle and thermodilution.[14] Blood flow in cerebral vessels is accurate because the magnetic resonance technique offers higher spatial resolution for vessel localization and cross-sectional area measurement. In an earlier report, we documented the use of this technique to study cerebral blood flow in women with eclampsia and severe

preeclampsia.[16] The study now presented was designed to calculate maternal cerebral blood flow longitudinally in pregnancy and then postpartum in a group of healthy women.

MATERIALS AND METHODS

This prospective study was designed to evaluate cerebral blood flow longitudinally during pregnancy and at 6 weeks postpartum in healthy women. Volunteers were recruited from University of Texas Southwestern Medical School or Parkland Memorial Hospital and were either employees or relatives of employees. This study was approved by The University of Texas Southwestern Medical School Institutional Review Board and signed informed consent was obtained. None had a history of chronic hypertension or a history of cerebrovascular abnormalities. Their medications included only prenatal vitamins and iron, and none were smokers. They were scheduled for magnetic resonance imaging at four time intervals: 14-16, 28-32, and 36-38 weeks' gestation, and again at 6-8 weeks postpartum.

Magnetic resonance imaging studies (Figures I - IV) were done using a 1.5T magnet (Signa Horizon LX NVI, GE, Milwaukee, WI). Using magnetization transfer contrast enhancement, the women, while supine, underwent a rapid two-dimensional time-of-flight (2D TOF) magnetic-resonance angiogram sequence (TR=22, TE=4, flip angle =20^{o}, NSA=1). The resulting magnetic resonance angiogram maximum intensity projection (MIP) was reconstructed from a data matrix of 64 slices (1.6 mm thickness, 18 cm FOV, 256 x 224 matrix). In order to ensure that the velocity images were obtained in a straight section of the artery under investigation, a scout image (TR=34, TE=17, flip angle = 20^{o}, 20 cm FOV, 512 x 256 matrix) perpendicular to the vessel in the circle of Willis visualized in the MIP was recorded for each artery. A peripherally gated phase contrast sequence (TR=34, TE=7, flip angle=40^{o}, 3 mm slice thickness, 20 cm FOV, 256 x 256 matrix) was applied lateral to the bifurcation of the internal carotid artery and perpendicular to the course of the artery as seen on the scout image to obtain velocity data. Velocity encoding was in the slice select direction with a set value of 120 cm/s. This range of encoded velocities has been found to be effective for measuring normal cerebral arterial flow velocities.[12,16]

Cerebral blood flow [Flow (mL/min) = vessel area (cm^2) x velocity (cm/min)] was determined at the bilateral proximal middle and posterior cerebral arteries. Flow measurements were analyzed using serial paired two-tailed Student t tests, which tested for flow differences between the 4 time intervals in each artery for each patient. Statistical significance was defined as $p<0.05$.

RESULTS

Of the 11 women recruited, one experienced significant claustrophobia and withdrew from the study. Another woman developed severe preeclampsia and her data were excluded from analysis. The other nine women, eight of Caucasian and one of African-American descent, remained normotensive and all delivered a term infant of 3477$\pm$547 grams. Five women were nulliparous; the mean age of the participants was 32.4$\pm$3.8 years. Shown in Table I are the means and standard errors for calculated flow at the four time intervals of the study. The p-values are shown in Table II. The values for the right and left middle cerebral arteries as well as for the right and left posterior cerebral arteries were averaged. Two women did not undergo the 36-38 weeks study due to missed appointments. Using postpartum values as the baseline non-pregnant blood flow, there was a significant decrease in flow in the middle cerebral arteries but not in the posterior cerebral arteries by the first examination at 14-16 weeks' gestation.

Table I. Cerebral blood flow at four time intervals

Cerebral Blood Flow (mL/min)				
Artery*	14-16 weeks	28-32 weeks	36-38 weeks	Postpartum (6-8 weeks)
MCA	135.2 ± 5.5	132.5 ± 4.6	118.2 ± 4.6	147.9 ± 5.0
PCA	52.4 ± 2.9	51.2 ± 2.4	44.2 ± 2.4	55.8 ± 2.7

* MCA = middle cerebral artery; PCA = posterior cerebral artery

Values are expressed as the mean ± Standard Error

Table II. Comparison of pairwise means for both cerebral arteries

Comparison of Pairwise Means for MCA		**PCA**
14-16 weeks – 28-32 weeks	p = 0.45	0.53
14-16 weeks – 36-38 weeks	p = 0.0002	0.004
14-16 weeks – nonpregnant	p = 0.001	0.29
28-32 weeks – 36-38 weeks	p = 0.004	0.005
28-32 weeks – nonpregnant	p = 0.005	0.20
36-38 weeks – nonpregnant	p < 0.0001	0.002

Flow remained unchanged by 28-32 weeks but decreased significantly again in late pregnancy for both the middle (Figure A) and posterior (Figure B) cerebral arteries. The diameter of the middle and posterior cerebral arteries showed no significant changes in any of the analyses, with a range of 2.43 to 2.49 mm for the middle cerebral arteries and 1.75 to 1.83 mm for the posterior cerebral arteries.

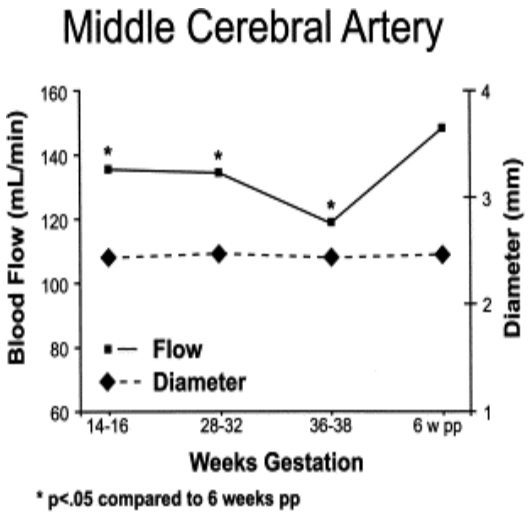

Figure A Middle cerebral arterial blood flow and vessel diameter determined longitudinally during pregnancy and compared with nonpregnant postpartum values in 9 healthy women

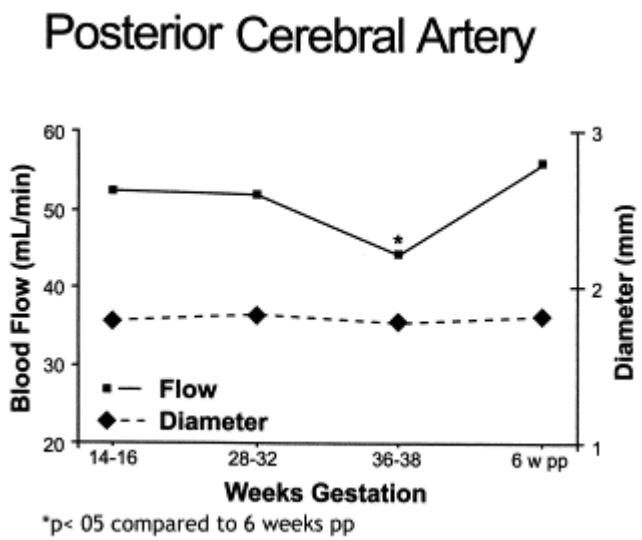

Figure B Posterior cerebral arterial blood flow and vessel diameter determined longitudinally during pregnancy and compared with nonpregnant postpartum values in 9 healthy women.

DISCUSSION

Most invasive methods used to determine cerebral blood flow, or those in which radioisotopes are used, cannot be used in normal pregnancy. Transcranial Doppler ultrasound is inaccurate to measure cerebral blood flow because vessel diameter cannot be measured.[17] In this study velocity-encoded phase-contrast MRI was used to ascertain blood flow longitudinally in normal pregnancy and again postpartum. This noninvasive technique is ideal for absolute blood flow determination because it allows precise vessel localization with cross-sectional area measurement, as well as velocity determination. Another advantage is the ability to determine blood flow in the posterior cerebral circulation not accessible by sonography.

Diameters of the middle and posterior cerebral arteries bilaterally remained unchanged throughout pregnancy and postpartum. Another seminal observation was that blood flow in the middle cerebral artery had decreased significantly by the end of the first trimester. Flow remained constant until 36-38 weeks at which time there was another significant fall at term. Taken together, this represents a 20 % decrease in blood flow at term, caused by a decrease in velocity and not large cerebral artery vessel diameter. The posterior cerebral artery showed significant changes in flow only in women near term and not as early as the middle cerebral artery. We believe this is secondary to the quantitatively lesser flow in the posterior circulation in the normal state and not secondary to redistribution. If we had a larger series of patients, we predict there would be a significant early changes in the posterior cerebral artery as well.

To our knowledge our study is the first in which magnetic-resonance imaging techniques have been used to measure cerebral blood flow longitudinally during pregnancy. The nonpregnant cerebral blood flow values in our study correspond well with those values of the only study that has used this technique to measure cerebral blood flow in nonpregnant subjects.[12] Our findings are in agreement with most studies in which middle cerebral arterial flow velocities were determined using transcranial Doppler.[3, 8-11] These investigators all documented decreased blood flow velocity as pregnancy advanced which suggests diminished flow assuming a constant vessel diameter.

One explanation for decreased cerebral blood flow in the large cerebral arteries during pregnancy is generalized vasodilation of the downstream resistance

vessels in the cerebral circulation in order to maintain a steady hemodynamic state. Burton and Burns have discussed the notion that around 40% of the resistance in the human circulation occurs at the level of distal arterioles.[17] Because middle and posterior arterial blood flow significantly decreases near term, in spite of normally rising mean arterial pressure and unchanged vessel diameter in the large cerebral arteries, we assume that the downstream resistance arterioles become more dilated in order to maintain constant blood flow at the tissue level.

Belfort et al [3] have corroborated this by showing that there is a progressive decrease in resistance index in the middle cerebral artery with advancing gestation as well as progressively decreased mean velocity. The reasons for these changes in cerebral blood flow in late pregnancy are unknown. Brackley et al [18] describes decreased vessel wall tone using transcranial doppler of the middle cerebral arteries as pregnancy progresses. 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.

The study provides physiological normative data of cerebral blood flow in two major regional arteries in both hemispheres during normal pregnancy. These data could be used to study abnormalities in cerebrovascular hemodynamics associated with preeclampsia and eclampsia. Using transcranial Doppler ultrasound, most investigators[2,4,5] have reported that blood flow velocity increases as preeclampsia develops and worsens. Increased resistance at the arteriolar level is widely felt to be the etiology of the increased velocity in this setting, either secondary to loss of autoregulation and hyperperfusion, or vasospasm and hypoperfusion. This is important as we have recently reported that eclamptic convulsions, but not usually severe preeclampsia, are associated with hyperperfusion and this may imply loss of autoregulation.[19] Our one patient who developed preeclampsia at 34 weeks did not demonstrate increased cerebral blood flow at 28 weeks, suggesting that such changes may occur later in pregnancy.

Using MR flow acquisition techniques, exquisite and accurate evaluation of the flow in large cerebral vessels is now possible in pregnancy. The potential of this technique to evaluate the underlying pathophysiology and to modify subsequent management of preeclampsia and eclampsia appears very promising.

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Chapter 4.

Increased cerebral blood flow in preeclampsia using magnetic resonance imaging

Zeeman GG, Hatab MR, Twickler DM.
Am J Obstet Gynecol 2004;191:1425-9

ABSTRACT

OBJECTIVE

To compare third trimester and non-pregnant cerebral blood flow of women with severe preeclampsia to normotensive controls using magnetic resonance imaging techniques.

STUDY DESIGN

Nine normotensive pregnant women and twelve untreated women with severe preeclampsia underwent velocity-encoded phase contrast magnetic resonance imaging of the bilateral middle and posterior cerebral arteries in the third trimester and at 6 to 8 weeks postpartum. Student t test was used for comparison with $p < 0.05$ considered significant.

RESULTS

Third trimester large cerebral artery blood flow was significantly higher in severe preeclampsia. Mean vessel diameter was unchanged except for the left posterior cerebral artery. There was no difference in mean vessel diameter or cerebral blood flow between the two groups while non-pregnant.

CONCLUSION

Cerebral blood flow is significantly increased in severe preeclampsia. We hypothesize that increased cerebral blood flow could ultimately lead to eclampsia through hyperperfusion and the development of vasogenic edema.

INTRODUCTION

Preeclampsia and eclampsia present with a specific constellation of neurological disturbances and neuroimaging lesions.[1] Cerebral lesions associated with preeclampsia-eclampsia were described anatomically by Sheehan and Lynch.[2] During the last decades these lesions have been characterized using both computed tomography and magnetic resonance imaging. Most often seen with eclampsia, the lesions usually represent areas of edema, but infarctions and thrombosis can also be seen.[3-9]

Over the years two major hypotheses have evolved to explain the development of cerebral lesions and grand mal seizures in eclampsia. The first theory emphasizes cerebrovascular overregulation with resulting extreme vasospasm and ischemia.[10,11] The second hypothesis centers around a failure of cerebrovascular autoregulatory mechanisms resulting in forced vasodilation, hyperperfusion, and vascular leakage with the subsequent development of reversible vasogenic edema some authors call hypertensive encephalopathy.[8]

Cerebral blood flow during pregnancy has been estimated using transcranial Doppler flow studies and normal pregnant women have been compared with preeclamptic women.[12,13] Transcranial Doppler data can not necessarily be extrapolated to represent cerebral blood flow nor the adequacy of cerebral perfusion because the caliber or cross-sectional area of the artery in question can not be measured. However, when flow velocity measurements are compared, there is increased velocity in preeclamptic women compared with normal pregnancies. Magnetic resonance imaging was shown to accurately measure cerebral blood flow in each vessel studied and we employed this technology to ascertain measurements in normal pregnant women and pregnant women.[9,14] In the present study we measured cerebral blood flow in women with preeclampsia to determine if hyperperfusion may play a role in the development of edema and infarctions in preeclampsia-eclampsia.

METHODS

Twelve patients who met the criteria for third trimester severe preeclampsia were recruited from the labor and delivery suite at Parkland Hospital before the onset of labor. Preeclampsia was defined according to the latest criteria of the National High Blood Pressure Education Program Working Group (new onset hypertension with persistent blood pressures $\geq$ 140/90 mmHg with $\geq$ 3+ protein on dipstick).[15] Women with sustained blood pressures $\geq$ 160/110 mmHg were excluded from participation secondary to the need for intravenous antihypertensive medication. Those with cerebral symptoms such as headache or scotomata were excluded in order not to delay initiation of magnesium sulfate therapy. None of the women received any drugs or fluid therapy prior to the imaging studies.

Nine healthy pregnant women were recruited amongst employees or relatives of employees from the University of Texas Southwestern Medical School or Parkland Memorial Hospital to serve as normotensive controls. None of the normotensive controls or women with preeclampsia had a history of chronic hypertension, or cerebrovascular abnormalities. Their medication only included prenatal vitamins and iron and none were smokers. Standard contraindications for magnetic resonance imaging were employed.

The cohort of preeclamptic women as well as the cohort of normotensive women were part of prior studies evaluating cerebral blood flow using magnetic resonance imaging techniques.[16] Study approval was obtained from the University of Texas Southwestern Medical School Investigational Review Board and all participants signed informed consent prior to enrolling in the study.

All women were studied on a 1.5T magnet (Signa Horizon LX NVI, GE, Milwaukee, WI) A single shot fast spin echo T2 weighted sequence in the axial plane was obtained first to document edema or other findings as later interpreted by a radiologist. A rapid three dimensional time of flight magnetic resonance angiogram sequence of the circle of Willis (TR=22, TE=4, flip angle = 20^{o}, NSA=1) using magnetization transfer contrast enhancement was performed with the resulting magnetic resonance angiogram maximum intensity projection reconstructed from a data matrix of 64 slices (1.6 mm thickness, 18 cm FOV, 256 x 224 matrix). Velocity images were then obtained of the proximal right and left middle cerebral arteries and right and left posterior cerebral arteries. In order to ensure that the velocity images

were obtained in a straight section of the artery under investigation, a scout image (TR=34, TE=17, flip angle = 20^{o}, 20 cm FOV, 512 x 256 matrix), perpendicular to the vessel in the circle of Willis visualized in the maximum intensity projection was recorded for each artery. A peripherally gated phase contrast sequence (TR=34, TE=7, flip angle = 40^{o}, 3 mm slice thickness, 20 cm FOV, 256 x 256 matrix) was applied lateral to the bifurcation of the internal carotid artery and perpendicular to the course of the artery as seen on the scout image to obtain velocity information. Velocity encoding was in the slice select direction with a set value of 120 cm/s. This range of encoded velocities has been found to be effective for measuring normal cerebral arterial flow velocities and should allow for the unambiguous measurement of higher velocities which are predicted in the event that significant vasospasm was found.[9,17]

A single shot fast spin echo T2 weighted sequence in the axial plane was used to document the presence or absence of cerebral edema. All study participants returned 6-8 weeks postpartum for a non-pregnant cerebral blood flow determination. Of the women with preeclampsia, one elected not to return due to claustrophobia and one was lost to follow-up.

Cerebral blood flow measurements [Flow (mL/min) = vessel area (cm^2) x velocity (cm/min)] were determined at the bilateral proximal middle and posterior cerebral arteries. Cerebral blood flow was analyzed with Student t tests to compare differences between the 2 groups at both time intervals in each artery for each patient. Statistical significance was defined as $p < 0.05$.

RESULTS

Cerebral blood flow was measured at a mean gestational age of 36.8 ± 2.6 weeks in the preeclampsia group, whereas this was 37.2 ± 1.0 weeks for the control group ($p = 0.67$). Mean birthweight was 2666 ± 673 grams in the preeclampsia group versus 3477 ± 527 grams in the control group ($p < 0.01$). Eight of the twelve women with preeclampsia were nulliparous, whereas this was the case for five of the nine controls. Systolic blood pressure in women with preeclampsia was 156 ± 9.7 and 100.5 ± 8.1 diastolic. All women in the control group remained normotensive. The T2 images of the preeclamptic women were without evidence of cerebral edema. In women with preeclampsia cerebral blood flow was significantly increased in all four vessels (Figure C), while, except for the left posterior cerebral artery, there was no change in mean blood vessel area (Figure D). Although there was a statistical significant difference in the left posterior artery mean diameter, the actual 0.14 mm difference between the two means is beyond the resolving capacity of the magnetic resonance imaging technique. There was no difference in cerebral blood flow nor mean vessel diameter between the two groups in the non-pregnant state (Figures E and F).

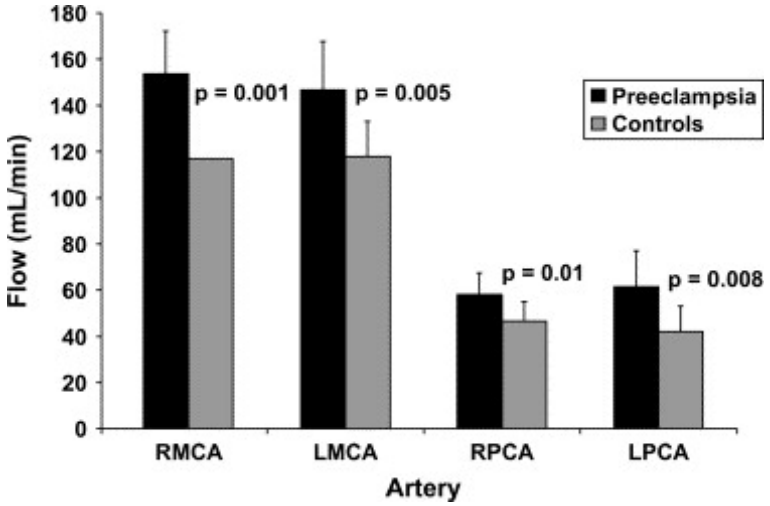

Figure C. Comparison of calculated blood flow in normotensive and women with preeclampsia in the third trimester. *Closed bars*, Preeclampsia group; *gray bars*, normotensive control subjects. *RMCA*, Right middle cerebral artery; *LMCA*, left middle cerebral artery; *RPCA*, right posterior cerebral artery; *LPCA*, left posterior cerebral artery.

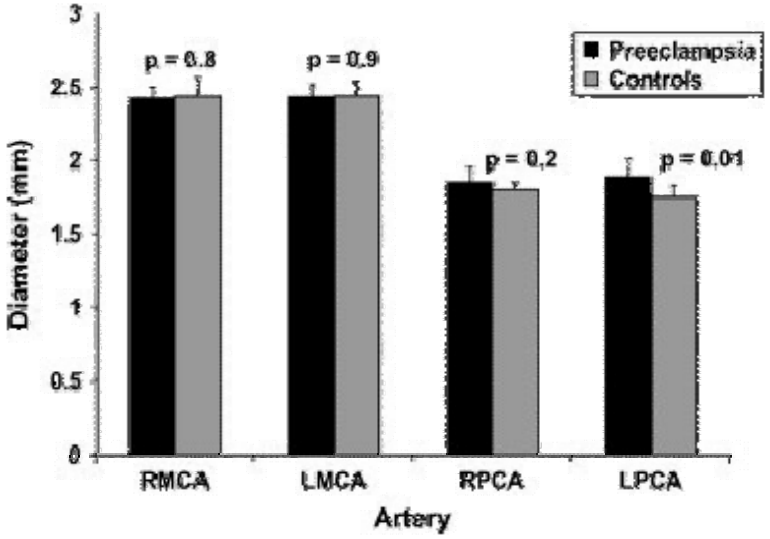

Figure D. Comparison of vessel diameter in normotensive and women with preeclampsia in the third trimester. *Closed bars*, Preeclampsia group; *gray bars*, normotensive control subjects. *RMCA*, Right middle cerebral artery; *LMCA*, left middle cerebral artery; *RPCA*, right posterior cerebral artery; *LPCA*, left posterior cerebral artery.

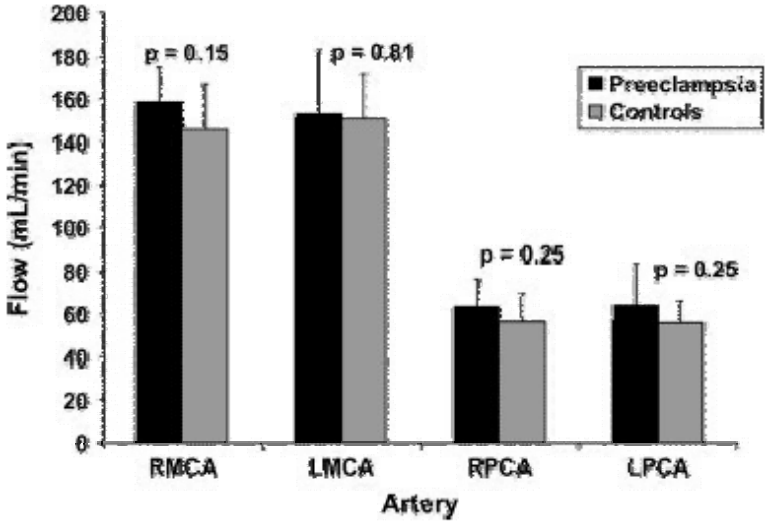

Figure E. Comparison of nonpregnant cerebral blood flow in normotensive and women with preeclampsia. *Closed bars*, Preeclampsia group; *gray bars*, normotensive control subjects. *RMCA*, Right middle cerebral artery; *LMCA*, left middle cerebral artery; *RPCA*, right posterior cerebral artery; *LPCA*, left posterior cerebral artery.

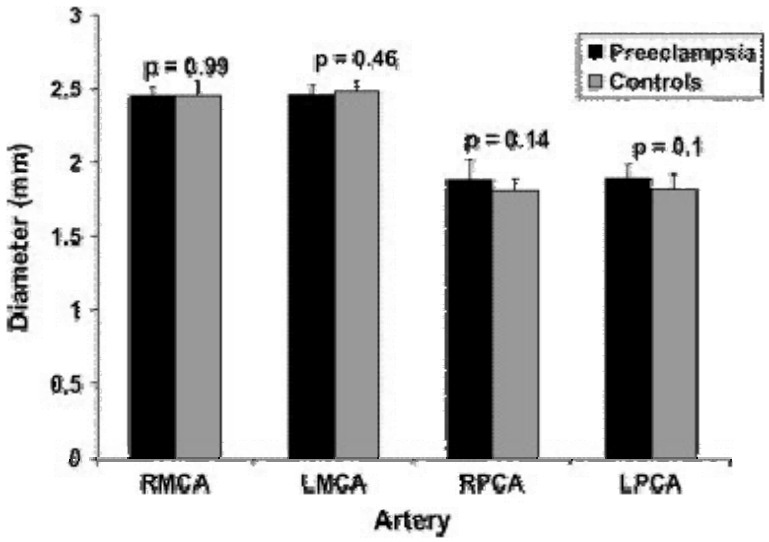

Figure F. Comparison of nonpregnant vessel diameter in normotensive and women with preeclampsia. *Closed bars*, Preeclampsia group; *gray bars*, normotensive control subjects. *RMCA*, Right middle cerebral artery; *LMCA*, left middle cerebral artery; *RPCA*, right posterior cerebral artery; *LPCA*, left posterior cerebral artery

DISCUSSION

Women with severe preeclampsia had a significantly increased cerebral blood flow at term when compared with normotensive controls in the third trimester. This increase in cerebral blood flow is not related to vasodilation of the major cerebral arteries because the diameter of the four main vessels was unchanged in preeclamptic women. These observations corroborate the findings of Belfort et al who used transcranial Doppler ultrasound studies to estimate cerebral blood flow using flow velocity.[12]

The strength of this study is with the use of magnetic resonance imaging technology that allows accurate assessment of flow in arteries arising form the Circle of Willis. In our previous study we found that cerebral blood flow was decreased significantly in late pregnancy compared with values determined two months postpartum.[14] Thus, the 20 percent increase in cerebral blood flow in severe preeclampsia is associated with levels similar to non-pregnant values. We can only speculate whether this increase is due to downstream vasodilation, increased cardiac output, increased mean arterial pressure, or local central nervous system factors of autoregulation.

Hypertensive encephalopathy is likely operative in some form in the genesis of cerebral lesions in eclampsia. The two theories of hypoperfusion secondary to vasospasm and hyperperfusion secondary to increased blood flow to explain the development of cerebral lesions in eclampsia may not be mutually exclusive. First, since in most cases cerebral edema is completely reversible, hyperperfusion that exceeds the retaining capacity of the brain capillary beds must be at play. Several investigators corroborated this by demonstrating increased cerebral perfusion pressures and/or increased blood flow velocities in women with preeclampsia compared with normotensive pregnant controls.[12,13,18] Other imaging techniques employed in preeclampsia also reinforce the hyperperfusion theory. Naidu applied a single photon emission CT scan to 63 eclamptic women and observed perfusion deficits in watershed areas of all subjects.[19] Second, that ischemia plays a role is now inarguable since infarcts develop in almost a fourth of eclamptic women.[3] Hypertensive encephalopathy is the clinical correlate of blood-brain barrier damage resulting from an acute rise in blood pressure. This is believed to be associated with a failure of autoregulatory mechanisms which, in turn, leads to passive

overdistension of the cerebral resistance vessels and to subsequent hyperperfusion.[20] Extravasation of fluids and proteins may occur resulting in vasogenic edema. Severe vasogenic edema may reduce cerebral perfusion to cause focal ischemia. This is likely because all areas of infarction seen in eclamptic women are encapsulated within areas of severe vasogenic edema.[3] Tamaki et al reported studies in hypertensive rats that also support this hypothesis.[21] They showed that minor degrees of cerebral edema were related to normal or increased cerebral perfusion whereas more marked areas of cerebral edema were accompanied by reduced perfusion with infarction. In addition to acute arterial hypertension systemic endothelial dysfunction and altered hemostasis might contribute to the pathogenesis of cerebral damage in hypertensive encephalopathy.[22] It is now widely accepted that preeclampsia and eclampsia are characterized by generalized endothelial cell activation.[23]

The findings now presented indicate that increased cerebral blood flow likely precedes the onset of convulsions. However, from our own clinical observations we know that women with chronic hypertension who present with significant hypertension but without proteinuria do generally not develop eclamptic convulsions. An intact endothelium appeared to be necessary in order to elicit the pressure dependent reduction of diameter in cat cerebral arteries to maintain cerebral autoregulation.[24] We therefore speculate that certain endothelial factors may play a role in preeclampsia that may not be occurring in women with significant chronic hypertension. It is these endothelial factors combined with elevated blood pressure and not elevated blood pressure alone that may result in the central nervous system edema that characterizes eclampsia. Indeed, Riskin and colleagues demonstrated that in chronically hypertensive women without preeclampsia increased mean arterial pressure did not result in increased cerebral blood flow velocity using transcranial Doppler ultrasound.[25] It may be a combination of the acuteness of the blood pressure rise “the delta change” and endothelial factors rather than the absolute blood pressure value that are the most important factors in the development of eclamptic convulsions.

We have become humbled by the complexity of the cerebrovascular circulation. Although we used the somewhat oversimplified equation of Flow = velocity X area, the physiology of this vascular bed is much more complex. On the one hand physiological factors affect cerebral blood flow that are not taken into

account. First is the dynamic pressure-flow relationship between the arterial blood pressure and intracranial pressure. Additional factors include the vascular smooth muscle and endothelial cells as well as the complex feedback system in the cerebral tissue. Changes in this system secondary to pregnancy are virtually unknown, although we do know that calculated flow in the large vessels of the brain decrease with increases in gestation.[14] Other factors affecting the cerebral circulation include metabolic and neurogenic influences, which are also governed by more or less variable feedback loops.[26] Oxygen extraction capability plays a major role as well.[27] Physical properties also come into play; rather than dealing with steady flow in a rigid tube we are dealing with pulsatile flow in branching blood vessels that have a variable compliance.

Our study finds increased blood flow calculations by MRI in the middle and posterior cerebral arteries of women with severe preeclampsia that is significantly different from normotensive controls. The increased blood flow in severe preeclampsia suggests a hyperperfusion model for cerebral edema, which in the setting of endothelial factors may interrupt the delicate balance between capillary and cellular perfusion pressures. Based on this information, the use of therapeutic agents that result in vasodilatation in this setting may be questioned. Our finding also stresses the importance of understanding the underlying hyperperfusion mechanism of preeclampsia before consideration of new treatment options.

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Chapter 5.

Cerebral infarction in eclampsia

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ABSTRACT

Objective

To characterize the neuroimaging findings of cerebral edema associated with eclamptic seizures using diffusion-weighted magnetic resonance imaging.

Study Design

During the 3-year period ending March 2002, 27 nulliparous women with eclampsia were evaluated with magnetic-resonance diffusion-weighted imaging and apparent diffusion coefficient mapping. Those with findings of restricted diffusion suggestive of cytotoxic edema underwent neuroimaging again 6 weeks postpartum.

Results

All but two of these 27 women (93 percent) had reversible vasogenic edema. Six were also found to have areas of cytotoxic edema consistent with cerebral infarction. Five of these six women had persistent imaging findings of infarction when studied postpartum, however, without clinical neurological deficits.

Conclusion

The spectrum of cerebral lesions in eclampsia as seen with magnetic-resonance imaging varies from initially reversible areas of vasogenic edema that may progress to cytotoxic edema and infarction in up to a fourth of women.

INTRODUCTION

The pathophysiology of the neurological disturbances in eclampsia is poorly understood. Particularly elusive is the association of hypertension with grand mal seizures and brain lesions characterized histopathologically by cortical and subcortical edema, petechial hemorrhages, and infarctions.[1] This is made even more enigmatic because eclamptic women generally appear to have full clinical recovery. To better understand the cerebrovascular mechanism(s) involved, a number of neuroimaging techniques have been used that include angiography,[2] computed-tomographic (CT) scanning,[3] magnetic resonance imaging (MRI),[4] and Doppler velocimetry.[5] With conventional CT- and MR-techniques, subcortical white matter and adjacent gray matter lesions consistent with edema are often seen.[3,4, 6,7] Abnormalities most frequently are located in the parieto-occipital lobes and correlate with the anatomical description of petechial hemorrhages and infarction.[1]

Based on these anatomical and imaging studies, two major hypotheses have evolved to explain the development of cerebral lesions and convulsions in eclampsia. In the first, eclampsia is attributed to lesions caused by cerebrovascular "overregulation" with extreme vasospasm that results in ischemia, cytotoxic edema, and infarction.[2,8] The second hypothesis is that lesions are caused by a loss of cerebrovascular autoregulation leading to hyperperfusion with subsequent interstitial or vasogenic edema.[5,9,10] Because eclampsia almost never causes permanent neurological sequelae, many presume that reversible vasogenic edema predominates.[4]

Within the past decade, magnetic resonance diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping were developed which facilitate the

discrimination between vasogenic and cytotoxic forms of cerebral edema.[11] This issue is critical because the former implies reversibility and the latter implies cerebral infarction. Of 10 eclamptic women studied with DWI and described in case reports, two had infarcts.[4,7,12-16] Because there have been no systematic studies, our purpose was to evaluate these techniques in women with eclampsia to characterize the relative frequency of vasogenic and cytotoxic edema.

MATERIALS AND METHODS

This study included nulliparous women with eclampsia defined as new-onset gestational hypertension accompanied by grand mal seizures. Standard management for severe preeclampsia and eclampsia has been detailed elsewhere.[17,18] Briefly, evaluation includes dipstick urine protein quantification, complete blood count, and measurement of serum levels of creatinine and aspartate transaminase. Women diagnosed with severe preeclampsia or eclampsia are given parenteral magnesium sulfate; intermittent hydralazine is given intravenously to lower blood pressures exceeding 160/110 mm Hg; and plans are made for delivery. Since April 1999, depending on availability of equipment, we began to routinely evaluate eclamptic women using cranial imaging studies that include magnetic-resonance diffusion-weighted imaging (DWI). This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. There were no evident neurologic deficits at time of the initial studies. For those with abnormal DWI results, follow-up imaging was planned at 6-8 weeks postpartum. None of these

women had a history of chronic hypertension and all were neurologically intact and normotensive 6 weeks postpartum.

All women underwent T1-weighted and fluid-attenuated inversion recovery (FLAIR) MRI scans within 36 hours after convulsions. Brain MRI was performed at 1.5 Tesla (General Electric LX NVI, Madison, WI) using sagittal T1-weighted images (500/9, TR/TE), field of view (FOV) of 20 x 20 cm, matrix 192 x 256, slice thickness 5 mm/0.5 mm gap, and 1 NEX; axial T1-weighted images (400/9, TR/TE), FOV 20 x 20 cm, matrix 224 x 256, slice thickness 5 mm/0.5 mm gap, and 1 NEX; and T2-weighted FLAIR images (8800/124/2200, TR/TE/TI), FOV 20 x 20 cm, matrix 224 x 256, slice thickness of 5 mm/0.5 mm gap, 1 NEX, and b=1000. Quantitative maps of apparent diffusion coefficients were computed using software provided by the vendor.

To understand the interpretation of the imaging data, a brief review of diffusion imaging is appropriate. DWI takes advantage of strong diffusion gradients that detect changes in water molecule distribution in cerebral tissue. In the presence of infarction, cytotoxic edema is caused by sodium pump failure and the resultant reduction in proton diffusion elicits hyperintense (“bright”) signal on DWI. Conversely, vasogenic edema is characterized by increased extracellular fluid with enhanced water diffusion and this may be seen as normal or decreased signal brightness on DWI. In some cases of vasogenic edema, however, hyperintense signal may be seen on DWI, dubbed “T2-shine through”[19] 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 apparent diffusion coefficient (ADC) in 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.

As part of the routine clinical practice at our institution, all images were initially read by neuroradiologists who were aware of the clinical indication for the study. For the purposes of this paper, all cases were re-read by the two radiologist authors in consensus (JLF, DMT). Cerebral infarction was presumed to be present by the demonstration of cytotoxic edema (restricted diffusion). Because we sought to characterize the frequency of cytotoxic edema, rather than to monitor its extent or severity, quantification of ADC was not performed.

For statistical comparisons, Chi-square and Student t-test were used. All tests were two-sided and statistical significance was inferred for p values less than 0.05.

RESULTS

During the 3-year interval, we evaluated 27 nulliparous women with eclampsia using diffusion-weighted MRI. Their mean age was 21.8 (± 6.5) years, and mean gestational age was 38.7 (± 2.4) weeks. There were 20 (74 percent) Hispanic women, 6 (22 percent) African-American women, and 1 (4 percent) white woman. Antepartum seizures occurred in 16 women while the remaining 11 had postpartum seizures. The MRI findings for these 27 women are summarized in Figure G. There were 25 who had cerebral edema on T2-weighted imaging involving the parieto-occipital gray-white junctions and the deep white matter (Figures 9 - 13). The brainstem, cerebellum, basal ganglia, and frontal lobes were less commonly affected

(Figures 14 – 17). Using DWI, hyperintense areas were identified in the parietal deep white matter in 15 of these 25 women. Vasogenic edema, characterized by increased ADC, was present in 12 of the 15 in whom ADC was available. Six of those 12 had concurrent foci of infarction evidenced by reduced ADC (restricted diffusion).

All six women with restricted diffusion detected by DWI studies at the time of their seizures were evaluated 6-8 weeks later with MR-imaging. Five of the six who initially had evidence of restricted diffusion had persistent hyperintense T2 lesions, presumably due to gliosis in response to infarction (Figures 9 - 13). The sixth woman had a normal follow-up study, implying that gliotic lesions were below discriminatory size for detection on MRI. It is also possible that this patient experienced transient ischemia because TIA is a syndrome that current data show can be positive on DWI in a high percentage of cases[38.]

We then compared the six women with cerebral infarctions with the other 18 women who were without evidence of infarction, i.e., 12 without abnormalities on DWI and 6 with hyperintense lesions on DWI but only increased ADC. As shown in Table 3, women with infarctions had clinical findings that suggested greater severity of the preeclampsia syndrome including "HELLP syndrome". Five of the six women with infarctions had one or multiple seizures prior to arrival at the hospital. This was true for only one of the other 18 women without infarctions.

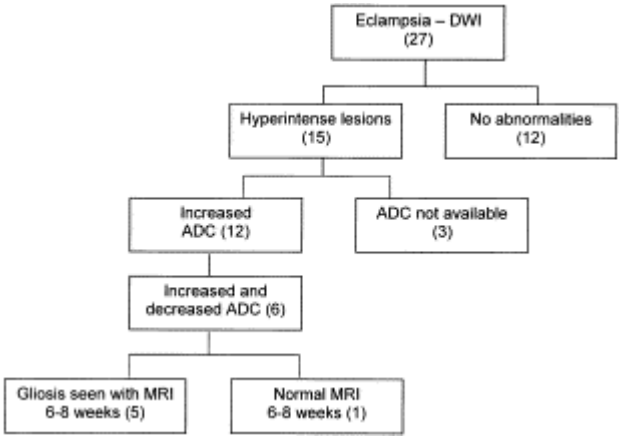

Figure G. Flow diagram of 27 nulliparous eclamptic women who underwent diffusion-weighted MRI. The number of patients is in parentheses. *DWI,* Diffusion-weighted imaging; *ADC,* apparent diffusion coefficient mapping.

Factor	Infarctions present (n=6)	Infarctions Absent (n=18)	P-value
Age (years)	23.0 ± 7.1	20.7 ± 6.4	0.465
Gestational age (weeks)	36.2 ± 2.4	39.0 ± 2.1	0.012
MAP[+] (mm Hg)	123 ± 10.8	112 ± 11.1	< 0.001
Δ MAP* (mm Hg)	40.4 ± 15.1	30.1 ± 11.7	0.096
Serum creatinine ≥ 0.9 mg/dL	4 (67%)	2 (11%)	0.007
Proteinuria ≥ 3+ (dipstick)	4 (67%)	3 (17%)	0.020
Platelet count (x 1000/μL)			
Mean	105 ± 53	203 ± 63	0.002
< 150	4 (67%)	4 (22%)	0.046
< 100	3 (50%)	1 (6%)	0.012
HELLP** syndrome	3 (50%)	1 (6%)	0.012
Multiple seizures	5 (83%)	2 (11%)	< 0.001

[+] MAP = maximal mean arterial pressure in proximity to seizure(s)

* Δ MAP = change in MAP from most recent prenatal visit compared with MAP proximate to seizure

** HELLP = hemolysis, elevated serum transaminase levels, low platelets.

Table 3. Comparison of Clinical Parameters That Indicate Eclampsia Severity in the Presence or Absence of Cerebral Infarctions

COMMENT

Eclampsia was associated with magnetic-resonance imaging (MRI) findings of cerebral edema in 93 percent of 27 nulliparous eclamptic women. These lesions typically, but not exclusively, involved the subcortical white and adjacent gray matter in the parieto-occipital lobes similar to that described by others.[6,7,15] Whereas most reports using diffusion-weighted MRI in eclampsia describe reversible vasogenic edema,[4,12-16] we found that almost a fourth of these women also have cerebral infarctions. The neuroimaging findings of these eclamptic women are remarkably similar to those described in nonpregnant patients with hypertensive encephalopathy.[15,21] They also correspond with classical histopathological studies[1] of brain lesions in eclampsia described as cortical and subcortical edema, petechial hemorrhages, and infarctions. In addition, neuropathological findings reported in nonpregnant individuals with fatal hypertensive encephalopathy resemble those described for eclampsia.[22] Thus, the “reversible posterior leukoencephalopathy syndrome”, as coined by Hinchey et al,[21] is not appropriate to describe the brain lesions imaged by MRI and CT in eclampsia and in nonpregnant patients with hypertensive encephalopathy. Specifically, these lesions are not confined to the posterior cerebrum. Also, our findings of infarctions with eclampsia, as well as data from nonpregnant subjects, support the view that reversibility cannot be assumed.[15]

Our data support the view that both mechanisms hypothesized to explain hypertensive encephalopathy are likely operative in some form in the genesis of cerebral lesions in eclampsia. Firstly, the high frequency of reversible vasogenic edema supports the work of most that edema results from hyperperfusion that exceeds the retaining capacity of the brain capillary beds.[4,5,9,10] Secondly, that ischemia plays a role is inarguable because infarcts develop in almost a fourth of

eclamptic women. While these infarctions have been attributed to vasospasm from cerebrovascular "overregulation",[2,8] we propose instead that severe vasogenic edema reduces 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. Tamaki et al.[23] reported studies in hypertensive rats that support this hypothesis. They showed that minimal degrees of focal cerebral edema were associated with normal to increased regional perfusion while marked focal edema was accompanied by decreased perfusion with infarction.

Our findings also confirm that eclampsia, like other forms of hypertensive encephalopathy, usually develops with blood pressures well within the range in which autoregulation assures normal blood flow.[10] Specifically, two-thirds of women now described had mean arterial pressures of 120 mm Hg or less. It has been shown that cerebral edema may develop with only mild hypertension when there is endothelial damage such as with hemolytic uremic syndrome, systemic lupus erythematosus, or immunosuppressive therapy.[15,24,25] This is important because it is now widely accepted that preeclampsia and eclampsia are characterized by generalized endothelial cell activation.[26] In this circumstance, the synthesis and secretion of a variety of endothelial cell and neutrophil chemokines and cytokines provoke a vicious cycle that results in disruption of vascular integrity. Thus, we agree with Schwartz et al[4] that cerebral edema in eclampsia develops from vascular leakage despite blood pressures well within the usual range of autoregulation. Meanwhile, multiple seizures occurred more often in those women who presented with higher blood pressures and other evidence of more severe preeclampsia.

There are limitations to our study. First, hyperintense lesions on DWI due to restricted diffusion were assumed to represent infarction. Other conditions have been

described in which restricted diffusion may occur,[27,28] and while cerebral abscess and tumor are not plausible, there is the possibility that parenchymal hemorrhage accounted for DWI hyperintensity. This is plausible because petechial hemorrhages are another common histopathological feature of eclampsia. This mechanism, however, is unlikely because restricted diffusion was reported only with large parenchymal hematomas[28] A second limitation is the possibility that intravenous magnesium sulfate or antihypertensive therapy had an effect on these cerebral lesions.

Cerebrovascular events in eclampsia appear to constitute a continuum characterized by an initial, reversible phase of vasogenic edema and seizures caused by hypertension along with endothelial dysfunction. Progressive edema leads to further neurologic deterioration including blindness, mental status changes, coma, transtentorial herniation, and death.[6,29] In this study, MRI documents a transition between reversible vasogenic edema to irreversible cerebral ischemia and infarction in a fourth of patients. Because widespread lesions due to vasogenic edema may be preceded by sudden blood pressure increases,[6] the importance of control of severe hypertension is emphasized.[18] Parenteral magnesium sulfate for the prevention and treatment of eclamptic seizures remains important as it is superior to traditional anticonvulsants for this use,[17] possibly due to neuroprotective properties during ischemia.[30] The prevention of the occurrence of multiple seizures seems important since the large majority of women with multiple seizures had evidence of cerebral infarction. Further studies that explore this possibility need to be undertaken. Finally, the high incidence of stroke in these women with eclampsia raises the possibility that they may develop at least a small degree of permanent brain dysfunction. Long-term clinical consequences, such as subtle brain dysfunction, need to be determined.

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Chapter 6.

The effect of magnesium sulfate on large cerebral artery blood flow in severe preeclampsia

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ABSTRACT

Objectives

To determine the effect of a 6 gram intravenous bolus of magnesium sulfate on maternal cerebral blood flow in women with preeclampsia.

Study Design

Velocity-encoded phase-contrast magnetic resonance imaging studies were performed on twelve preeclamptic women prior to and immediately after infusion of a 6 gram magnesium sulfate loading dose. Cerebral blood flow was determined at the bilateral proximal middle and posterior cerebral arteries. Study participants returned 6 weeks postpartum for a non-pregnant measurement of cerebral blood flow. The Wilcoxon paired-sample test was used with statistical significance defined as $p < 0.05$.

Results

There was no significant difference in cerebral vessel diameter nor blood flow for any of the examined arteries between the pre- and post magnesium sulfate therapy states.

Conclusions

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 question the role of magnesium sulfate as a vasodilator of these arteries.

INTRODUCTION

Magnesium sulfate ($MgSO_4$) therapy has been used successfully for many years in the USA for the prevention and treatment of eclamptic seizures [1]. There remains controversy about this course of treatment since $MgSO_4$ is not a proven anticonvulsant. However, there is sufficient evidence to suggest that $MgSO_4$ is more effective for the prevention of eclampsia than traditional anticonvulsants such as phenytoin and diazepam. In addition, $MgSO_4$ is more effective than placebo or nimodipine, a calcium antagonist believed to have specific cerebral vasodilatory properties [2-5].

Two major hypotheses have evolved to explain the development of convulsions in eclampsia. In the first, eclampsia is attributed to lesions caused by cerebrovascular “overregulation” with extreme vasospasm that results in ischemia, cytotoxic cerebral edema and infarction [6,7]. The second hypothesis is that eclampsia is caused by a loss of autoregulation leading to hyperperfusion with subsequent interstitial or vasogenic cerebral edema [8,9].

In this study, velocity-encoded phase-contrast magnetic resonance imaging (MRI) was utilized to measure both velocity and vessel diameter in the intracerebral circulation in women with preeclampsia before and after $MgSO_4$ therapy. Such accurate determination of cerebral blood flow in the large intracranial arteries would confirm the presence, if any, of vasospasm and its resolution after treatment. If eclampsia is due to cerebral vasospasm then $MgSO_4$ may have some vasodilatory properties inducing alterations in blood flow in the large cerebral arteries. If however, eclampsia is associated with hyperperfusion and ensuing focal vasogenic edema, then cerebral blood flow may not be altered after treatment with $MgSO_4$.

MATERIALS AND METHODS

Twelve patients with preeclampsia were recruited from the labor and delivery suite at Parkland Hospital. Preeclampsia was defined according to the latest criteria of the National High Blood Pressure Education Program Working Group (new onset hypertension with persistent blood pressures $\geq$ 140/90 mmHg with $\geq$ 3+ protein on dipstick) [10]. Women with sustained blood pressures $\geq$ 160/110 mmHg were excluded from participation secondary to the need for intravenous antihypertensive medication. Those with cerebral symptoms such as headache or scotomata were excluded in order not to delay initiation of $MgSO_4$ therapy. Women with a history of chronic hypertension or neurologic disorders were excluded as well. None of the women received any drugs or fluid therapy prior to initiation of the study.

All women were studied on a 1.5T magnet (Signa Horizon LX NVI, GE, Milwaukee, WI) after signing an informed consent document approved by the University of Texas Southwestern Medical Center Institutional Review Board. A single shot fast spin echo T_2 weighted sequence in the axial plane was obtained first to document edema or other findings as later interpreted by a radiologist. A rapid three dimensional time of flight magnetic resonance angiogram sequence of the circle of Willis (TR=22, TE=4, flip angle = 20^o, NSA=1) using magnetization transfer contrast enhancement was performed with the resulting magnetic resonance angiogram maximum intensity projection reconstructed from a data matrix of 64 slices (1.6 mm thickness, 18 cm FOV, 256 x 224 matrix). Velocity images were then obtained of the proximal right and left middle cerebral arteries and right and left posterior cerebral arteries. In order to ensure that the velocity images were obtained in a straight section of the artery under investigation, a scout image (TR=34, TE=17, flip angle = 20^o, 20 cm FOV, 512 x 256 matrix) along the long axis of the vessel in the circle of Willis visualized in the maximum intensity projection was recorded for each artery. A peripherally gated phase contrast sequence (TR=34, TE=7, flip angle = 40^o, 3 mm slice thickness, 20 cm FOV, 256 x 256 matrix) was applied perpendicular to the course of the artery as seen on the scout image to obtain velocity information. Velocity encoding was in the slice select direction with a set value of 120 cm/s (Figure 1 - 4). This range of encoded velocities has been found to be effective for measuring normal cerebral arterial flow velocities [11] and should allow for the

unambiguous measurement of higher velocities which are predicted in the event that significant vasospasm was found.

After this first magnetic resonance imaging study set which lasted a total of 20 minutes was completed, the women were given 6 grams of $MgSO_4$ intravenously over a 20-minute period, directly after which an identical 20 minute imaging sequence as the pre-treatment one was repeated. Upon completion of the study the patient was transported back to the labor and delivery suite for delivery. Magnesium sulfate infusion was continued per protocol at 2 grams/hour until 24 hours postpartum. Study participants returned 6-8 weeks postpartum for a non-pregnant cerebral blood flow determination. One patient elected not to return due to claustrophobia and one was lost to follow-up.

Cerebral blood flow measurements [Flow (mL/min) = vessel area (cm^2) x velocity (cm/min)] were analyzed with a Wilcoxon paired-sample signed-ranks test which tested for differences between the pre-$MgSO_4$, post-$MgSO_4$ and follow-up studies in each artery for each patient. Statistical significance was defined as $p < 0.05$.

RESULTS

Some clinical characteristics of the twelve women with preeclampsia are shown in Table 4. Eight were nulliparous. The mean gestational age at delivery was 36.8 ± 2.6 weeks.

Flow data was not obtained in the posterior cerebral arteries of one patient due to excessive motion. Using a Wilcoxon paired-sample signed-ranks analysis, there was no significant difference in blood flow between the pre- and post-$MgSO_4$ studies (Table 5). In addition, there was no significant difference in flow in any of the arteries when the pre-$MgSO_4$ and postpartum studies were compared (p-values 0.38, 0.28, 0.11, and 0.77 for the right and left MCA, and the right and left PCA, respectively).

The same holds true for vessel diameter. There was no significant difference in vessel diameter between the pre- and post- $MgSO_4$ studies (Table 6, Figure 14). In addition, there was no significant difference in diameter in any of the arteries when

the pre-$MgSO_4$ and postpartum studies were compared (p-values 0.16, 0.56, 0.63, and 0.99 for the right and left MCA, and the right and left PCA, respectively).

No evidence of edema was seen on the T_2 weighted image; edema would be seen as increased signal intensity on these images. There was no change in the diameter of the large vessels of the Circle of Willis to suggest vasospasm or vasodilation. Based on the MRI velocity image resolution, the minimum detectable change in vessel diameter was calculated to be 20%. Thus, probability testing at the 0.05 level of significance to detect a 20 % difference in flow compared with the postpartum study revealed a power of 93-99% for the right and left middle cerebral arteries and right posterior cerebral artery, but 60% for the left posterior cerebral artery.

	Mean $\pm$ SD
Age (years)	23.5 $\pm$ 6.2
Gestational age (wks)	36.8 $\pm$ 2.6
Birthweight (grams)	2666 $\pm$ 673
Systolic BP (mmHg)	156 $\pm$ 9.7
Diastolic BP (mmHg)	100.5 $\pm$ 8.1
Hematocrit (%)	33.4 ± 4.2
Platelets ($x10^3/mm^3$)	224 ± 49
AST (Aspartate Aminotransferase) (IU/L)	0.6 ± 0.1
Creatinine (mg/dL)	29.0 ± 27.2

Table 4. Clinical characteristics of 12 women with severe preeclampsia

	Right MCA	Left MCA	Right PCA	Left PCA
Pre-$MgSO_4$	154.0 (17.2)	147.0 (21.0)	58.2 (9.2)	61.7 (15.6)
Post-$MgSO_4$	154.2 (28.8)	147.6 (22.7)	60.1 (9.1)	62.2 (20.3)
6 w postpartum	158.7 (16.3)	153.4 (29.5)	63.3 (13.0)	64.0 (19.4)
p-value*	0.79	0.99	0.83	0.73

* p-value comparing pre- and post $MgSO_4$ values

Table 5. Mean calculated flow (mL/min) and standard deviations for all examined arteries.

	Right MCA	Left MCA	Right PCA	Left PCA
Pre-$MgSO_4$	2.42 (0.08)	2.42 (0.09)	1.85 (0.10)	1.89 (0.12)
Post-$MgSO_4$	2.42 (0.13)	2.39 (0.05)	1.86 (0.16)	1.85 (0.15)
6 w Postpartum	2.45 (0.06)	2.46 (0.07)	1.88 (0.12)	1.90 (0.08)
p-value*	0.97	0.21	0.85	0.57

* p-value comparing pre- and post $MgSO_4$ values

Table 6.

Mean vessel diameter (mm) and standard deviations for all examined arteries.

DISCUSSION

In this study we used a velocity-encoded phase-contrast magnetic resonance imaging technique to measure cerebral blood flow in women with preeclampsia before and after administration of $MgSO_4$ as well as postpartum. The middle cerebral and posterior cerebral arteries were the ones studied because of the high velocity of the middle cerebral artery and the clinical findings in eclampsia suggesting symptoms related to the posterior circulation. We found that cerebral blood flow and the caliber of these arteries did not change with administration of $MgSO_4$.

To better understand the cerebrovascular mechanism(s) involved in the pathophysiology of eclamptic convulsions, a number of neuroimaging techniques have been used that include cerebral angiography [6,7], computed tomography [6,12,13], MRI [11] and Doppler velocimetry [8]. Of the techniques listed, only phase-contrast MRI is an established method of accurately measuring both velocity and arterial cross sectional area, the two quantities required for the accurate determination of blood flow [11,14]. A prior phase-contrast MRI study from our institution [11] showed no significant difference in either the middle or posterior cerebral artery blood flow in women with eclampsia and severe preeclampsia between their acute postpartum and delayed baseline follow up studies, as well as compared to their normal cohorts. The blood flow was unchanged despite the presence of remarkable brain lesions in all 8 women with eclampsia. However, all the subjects in that study were examined after receiving $MgSO_4$. Thus, in spite of the findings of varying levels of severity of edema on MRI, it is possible that any vasospasm could have resolved by the treatment and therefore, before blood flow was measured. In the current study, women with preeclampsia were examined before and immediately after receiving a therapeutic bolus of $MgSO_4$ so that any acute vasodilatory effects of magnesium could be assessed.

Previous studies evaluating the effects of $MgSO_4$ on the cerebral circulation in preeclampsia have mainly used transcranial Doppler ultrasound. One group reported no significant differences in antepartum (before $MgSO_4$ administration) and postpartum (after $MgSO_4$ discontinuation) mean middle cerebral artery flow velocity in a group of 46 women with preeclampsia [15]. Another study evaluated the antepartum middle cerebral artery before and after $MgSO_4$ administration and found no changes in flow velocity, but a significant decrease in pulsatility index was noted

which led the investigators to speculate that $MgSO_4$ acted to vasodilate more distal vessels [16]. In another study, the blood velocity of the middle cerebral artery in 12 preeclamptic patients was observed to increase in reponse to $MgSO_4$ therapy [17], whereas a later study suggests that middle cerebral artery velocity decreases in the 13 eclamptic women who received a loading dose of 4 grams $MgSO_4$ [18]. Major limitations of transcranial Doppler ultrasound are its inability to measure vessel cross sectional area and therefore true blood flow [19,20]. Typically, blood flow is inferred from velocity and other mathematically derived indices.

The lack of any statistically significant change in either the diameter or flow after the administration of $MgSO_4$ in this study suggests it may not act as an arterial vasodilator of large vessels in preeclampsia. Current MRI technology does not permit the accurate evaluation of flow in smaller, downstream arterioles. Even though the mean change in blood flow was not significant, it is possible that some of the smaller arterioles responded with vasodilation while others did not. Indeed, the occurrence of ischemia may be secondary hyperperfusion rather than hypoperfusion. Vasogenic edema secondary to hyperperfusion is seen in hypertensive encephalopathy and seems to play an important role when eclampsia develops [8,9]. The neuroimaging findings of women with eclampsia are remarkably similar to those described in non-pregnant patients with hypertensive encephalopathy [13,21]. In addition, neuropathological findings reported in non-pregnant individuals with fatal hypertensive encephalopathy resemble those described for eclampsia [22].

Some limitations to our study should be addressed. First, while phase-contrast MRI is suitable for evaluating blood flow in the large cerebral arteries, it does not measure blood flow in the more downstream resistance arterioles where changes in diameter may occur in response to the instituted therapy. Due to the limitations in resolution imposed by the MR sequence parameters, if such changes did occur in the diameters of the more distal vessels, it is very likely that our technique missed any resulting changes in blood flow in the proximal large cerebral arteries of less than 20 %. In comparison, other studies, which did detect a change in MCA flow in preeclamptic women pre- and post $MgSO_4$ infusion, have reported increases of 32 % in blood velocity. Second, this study excluded the most severe of the preeclamptic patients such as those with headache and/or scotoma. Also, women with blood pressures exceeding 160/110 mmHg required immediate initiation of antihypertensive therapy, which would confound cerebral blood flow studies. Since

the process of obtaining informed consent, transporting and imaging the patients took close to 2 hours, it was felt that their therapy could not be delayed for that long and thus they were excluded from the study. Third, it is known that the effects of $MgSO_4$ peak almost immediately after administration [23]. We particularly chose to repeat the study at the end of the bolus infusion because serum concentrations of Mg^{2+} are maximal at that time [24]. In addition, our patients showed the typical side effects of a bolus infusion such as flushing. The MRI determination of flow for each artery was performed at one moment in time and any effects of $MgSO_4$ that did not coincide with that time-window were probably missed. Last, we report this study having only 12 study participants. Power analysis after the 12th woman had enrolled revealed sufficient power to conclude that there is no change in cerebral blood flow after administration of $MgSO_4$ in the right and left MCA and the right PCA. There was insufficient power to conclude the same for the left PCA. Our explanation for the differential behavior of this vessel is that during the study protocol this was always the last of the 4 blood vessels to be examined. Patient fatigue and motion likely played a role in obtaining reliable measurements.

In summary, our findings suggest that $MgSO_4$ does not act by means of direct vasodilation of the large cerebral arteries, challenging the vasoconstriction model for symptoms of preeclampsia and eclampsia. Until further studies of the mechanism of preeclampsia and eclampsia are performed, $MgSO_4$ remains the therapy of choice for the control and prevention of eclamptic convulsions, based on its clinical effectiveness in several trials [2-5].

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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 occurence 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 subarachnnoid 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 myelinolyis (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 pathophysiological 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 longterm 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 longterm 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. Wih 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 leisons 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.

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Samenvatting

Hoofdstuk 1 Preeclampsie blijft een van de meest onopgeloste problemen in de obstetrie ondanks belangrijke progressie betreffende het ontrafelen van de pathofysiologie in de laatste jaren. Wereldwijd overlijden naar schatting 50-65.000 preeclamptische vrouwen per jaar; meestal aan de gevolgen van cerebrale complicaties zoals intracraniele bloedingen. Zwangerschap induceert substantiële fysiologische hemodynamische veranderingen met tot op heden onduidelijke impact op de cerebrale hemodynamiek. De huidige opvatting en behandeling van hypertensieve aandoeningen tijdens de zwangerschap zijn gebaseerd op het paradigma dat preeclampsie kan evolueren van mild tot ernstig en, uiteindelijk, preeclampsie. Hiermee wordt aangenomen dat de kans op een eclamptisch insult afhankelijk is van de ernst van de symptomen. Het is echter de vraag of dit een juiste interpretatie is; het optreden van een eclamptisch insult is immers niet altijd goed voorspelbaar aan de hand van traditionele klinische factoren zoals de hoogte van de bloeddruk. Er is nagenoeg niets bekend betreffende de mogelijke aanpassingen van de cerebrale autoregulatie ten tijde van de gezonde dan wel de hypertensieve zwangerschap. Sinds de afgelopen decennia bestaan er twee hypothesen betreffende de ontwikkeling van het tonisch-clonische insult bij preeclampsie. De eerste theorie benadrukt het fenomeen van vasospasme en ischemie, als het ware cerebrale “overregulatie”. De tweede theorie focust op het falen van de cerebrale mechanismen van autoregulatie welke vervolgens resulteren in geforceerde cerebrale vasodilatatie, hyperperfusie en het ontstaan van reversibel vasogeen oedeem ten gevolge van extravasatie. Dit laatste mechanisme ligt ook ten grondslag aan het fenomeen van hypertensieve encephalopathie en wordt tegenwoordig ook wel aangeduid met “reversible posterior leukoencephalopathy syndrome “ (RPLS). Beide mechanismen kunnen resulteren in het ontstaan van cerebraal oedeem, echter met geheel verschillende kenmerken. Dit proefschrift probeert door middel van het gebruik van moderne MRI technieken meer inzicht te verschaffen in de cerebrale hemodynamiek van de normale evenals de hypertensieve zwangerschap.

De cerebrale circulatie is in vele opzichten uniek. Een van de belangrijkst geachte fenomenen is het ontbreken van precapillaire sfincters; de regulatie van de vaatweerstand wordt derhalve hoofdzakelijk gereguleerd door de arteriele en

arteriolaire segmenten. Het meest bekende verschil tussen de systemische en cerebrale circulatie is de aanwezigheid van de bloed-hersenbarriere. De aanwezigheid van zogenaamde “tight junctions”” is specifiek vor het cerebrovasculaire endotheel. De aanwezigheid van hormonale effecten op de endotheel-afhankelijke cerebrale vasodilatatie is inmiddels aangetoond. Dit betekent wellicht dat zwangerschap gepaard gaat met veranderingen in de cerebrale circulatie die het cerebrum meer of minder gevoelig maken voor geforceerde vasodilatatie en hyperperfusie in geval van acute hypertensie.

Hoofdstuk 1 gaat eerst in op de basisprincipes van de MRI technologie. Deze techniek is gebaseerd op het fenomeen van kernspinresonantie; het intrinsieke magnetisme van elke individuele nucleus. Dit intrinsieke magnetisme kan gemanipuleerd worden door een extern magneetveld gekenmerkt door uiterst precieze kenmerken betreffende de functies van richting en tijd. De mate van contrast hangt af van het weefseltype en van de werkingsduur van het externe magneetveld op het intrinsieke magnetisme van de nucleus. Men kan zogenaamde T1-gewogen beelden verkrijgen waarin liquor (hersenvocht) en waterrijke structuren donker overkomen. Daarentegen zijn deze op T2-gewogen beelden juist wit. De diffusie-gewogen MRI techniek geeft de willekeurige diffusiebewegingen van watermoleculen weer. Deze is afhankelijk is van de fysiologische en anatomische omstandigheid van het molecuul. De diffusiebeweging kan met behulp van deze techniek gekwantificeerd worden; de zogenaamde apparent diffusion coefficient (ADC0. De detectie van het hyperacute ischemische cerebrovasculaire accident (CVA) vormt op dit moment de belangrijkste klinische applicatie van deze diffusietechniek in de geneeskunde. Deze techniek differentieert reversibel vasogeen oedeem (toegenomen diffusie) van irreversibel cytotoxisch oedeem (afgenomen diffusie).

De autoregulatie van het cerebrale vasculaire netwerk is extreem complex en wordt beïnvloed door vele factoren betreffende de fysische eigenschappen van pulsatiele flow van een complexe vloeistof. Daarbij komt dat het brein een moeilijk toegankelijk orgaan is. Derhalve is er weinig kennis omtrent de fysiologische veranderingen welke door de zwangerschap worden uitgelokt. Transcraniele Doppler echoscopie is de meest gebruikte non-invasieve methode om de cerebrale circulatie te bestuderen. Deze techniek geeft informatie omtrent de veranderingen in de bloedstroomsnelheid, welke, samen met kennis van de systemische bloeddruk, een

inschatting geeft over de cerebrale perfusie en de cerebrovasculaire weerstand in de meer distaal gelegen arteriolen. Echter, de interpretatie van Doppler indices, zoals de pulsatility index, ten behoeve van uitspraken omtrent de cerebrovasculaire weerstand, is afhankelijk van een aantal a-priori aannames. Bijvoorbeeld omtrent de vasculaire compliance welke gerelateerd is aan de elasticiteit van de vaatwand, evenals de rheologische eigenschappen van het bloed. Ook kan er met de Doppler techniek geen uitspraak worden gedaan over de **absolute** bloeddoorstroming van de cerebrale vaten daar de actuele diameter niet gemeten kan worden. Verscheidene Doppler studies in gezonde zwangere vrouwen vertonen een afname van de gemiddelde bloedstroomsnelheid naarmate de zwangerschap vordert. Veronderstelt wordt dat dit secundair is aan verminderde vasculaire weerstand, hetgeen zou impliceren dat er sprake is van distale arteriolaire vasodilatatie. Bij preeclampsie wordt juist een toename van de bloedstroomsnelheid gezien, hetgeen het vasospasme model voor de etiopathogenese van eclampsie steeds in stand heeft gehouden. Het is echter de vraag of deze extrapolatie juist is.

Velocity-encoded phase-contrast MRI is een recent ontwikkelde methode die wel gebruikt wordt om de **absolute** bloeddoorstroming te meten. Deze methode is gebruikt voor het meten van de bloeddoorstroming in de intracraniele, renale en cardiopulmonale circulaties en laat een goede correlatie zien met traditionele invasieve methoden zoals verkregen tijdens bijvoorbeeld hartkatheterisatie. Het feit dat waterstofkernen in het bloed, zodra zij een magnetisch veld passeren een faseverandering ondergaan proportioneel aan hun bloedstroomsnelheid, ligt ten grondslag aan het principe van deze techniek. De **absolute** bloeddoorstroming wordt dan berekend door vermenigvuldiging van de bloedstroomsnelheid met de oppervlakte van het bloedvat. SPECT (Single Photon Emission Computed Tomography) en spectroscopie zijn op kleine schaal wel gebruikt om de veranderingen in regionale cerebrale doorbloeding cq. metabolisme te karakteriseren in de gezonde zwangerschap alsmede in preeclampsie. De bevindingen lopen nogal uiteen hetgeen de moeilijkheid van het interpreteren van de cerebrovasculaire mechanismen in (pre)-eclampsie illustreert.

Waarom specifiek het cerebrum bij sommige vrouwen met preeclampsie wel is betrokken en bij anderen niet is onduidelijk en is een van de belangrijkste vragen in preeclampsie research in de komende jaren. Hoofdstuk 3 t/m 6 presenteren enig voorlopig onderzoek op dit gebied en proberen een aantal grote vragen te

beantwoorden. Ondanks dat het aantal patiënten welke in deze studies worden geëvalueerd gelimiteerd lijkt te zijn, zijn het in de context van het geringe voorkomen van eclampsie toch studies van formaat en zijn de resultaten van de studies van klinische betekenis.

Hoofdstuk 2 geeft een overzicht van het beeldvormend onderzoek van het cerebrum bij preeclampsie en probeert dit te relateren aan de pathogenese van de cerebrovasculaire verstoringen. Hiertoe werd Pubmed doorzocht met het gebruik van de sleutelwoorden ” preeclampsie”, “eclampsie”, “Computed tomography (CT)”, en “ Magnetic resonance imaging (MRI)”, in de periode 1980 - 2004. De referenties van alle artikelen werden nadien eveneens doorzocht. CT en MRI studies demonstreren transiente laesies in de (sub)-corticale gebieden met name van de parietale-occipitale hersenkwabben, de basale ganglia en/of hersenstam, overeenkomende met oedeem. Onder welke omstandigheden dit optreedt onbekend maar lijkt niet noodzakelijkerwijs afhankelijk te zijn van de absolute hoogte van de bloeddruk; de mate en het tempo van de bloeddrukstijging alsmede de aanwezigheid van endotheeldysfunctie lijken wel bevorderlijk. Eclampsie lijkt het eindstadium te zijn van minstens 2 pathofysiologisch verschillende mechanismen: primaire vasospasme versus cerebrale hyperperfusie met als gevolg geforceerde vasodilatatie. Wanneer beeldvorming gewenst is kan het gebruik van de MR diffusie-gewogen techniek het cerebrale oedeem verder karakteriseren. Op basis van de cerebrale afwijkingen bij beeldvormend onderzoek is de aandacht gericht op Reversible Posterior Leucoencephalopathy syndrome (RPLS) als een model voor de cerebrale afwijkingen in eclampsie. De 2 condities vertonen vele overeenkomsten, zowel in pathologisch, radiologisch, alsmede klinisch opzicht.

Hoofdstuk 3 beschrijft een prospectieve longitudinale studie van de cerebrale doorbloeding tijdens de zwangerschap alsmede 6 weken postpartum in gezonde vrouwen. De studie levert fysiologische normatieve data betreffende de cerebrale doorbloeding in 2 grote regionale arterieen in de beide hemisferen. Tien gezonde zwangere vrijwilligers ondergingen velocity-encoded phase-contrast MRI op 3 tijdstippen tijdens de graviditeit: 14-16, 28-32, 36-38 weken amenorroeduur alsmede 6-8 weken postpartum. Statistische analyse bestond uit opeenvolgende gepaarde Student t-testen, waarbij $P < 0.05$ was gedefinieerd als statistisch significant. De niet-zwangere waarden zijn gebruikt ter vergelijking. Bij 14-16 weken amenorroeduur nam de cerebrale doorbloeding in de arteria cerebri media af maar was niet significant veranderd in de arteria cerebri posterior. De doorbloeding bleef daarna constant tot 36-38 weken amenorroeduur waarna er een volgende significante daling plaatsvond. Cumulatief betekent dit een 20 % daling in cerebrale doorbloeding in de a terme periode vergeleken met de niet-zwangere conditie. Dit werd specifiek veroorzaakt door een vermindering van de bloedstroomsnelheid en niet door een verandering van de diameter van de grote cerebrale vaten. De doorbloeding van de arteria cerebri posterior liet alleen een significante daling zien in de a terme periode en dus niet zo vroeg in de zwangerschap vergeleken met de arteria cerebi media. Deze bevindingen ten aanzien van de bloedstroomsnelheid komen overeen met de meeste transcraniele Doppler studies in de gezonde graviditeit. Een verklaring voor de afname van de cerebrale doorbloeding in de grote cerebrale arterieën in de graviditeit is niet gemakkelijk te geven. Het lijkt voor de hand te liggen dat tijdens de zwangerschap een gegeneraliseerde vasodilatatie van de distale arteriolen in de cerebrale circulatie ontstaat ter handhaving van een hemodynamisch stabiele situatie. Het is interessant te speculeren dat locale veranderingen in de cerebrale autoregulatie het gevolg kunnen zijn van veranderde vasculaire respons op cq. Biologische beschikbaarheid van, vasoactieve mediatoren zoals prostacycline, nitric oxide en angiotensine-II zowel als een variatie van andere mediatoren, zoals progesteron, secundair aan de zwangerschap. Tevens zou de zwangerschap kunnen resulteren in een toename van de cerebrale zuurstof extractie capaciteit.

Hoofdstuk 4 vergelijkt de cerebrale doorbloeding van zowel preeclamptische als normotensieve vrouwen met behulp van velocity-encoded phase-contrast MRI in het 3e trimester van de zwangerschap alsmede in de niet-zwangere periode. Twaalf patiënten met preeclampsie in het 3e trimester alsmede negen normotensieve zwangere vrouwen ondergingen metingen van de cerebrale doorbloeding in de arteriae cerebri mediae en posteriores. Vrouwen met preeclampsie hadden een significant toegenomen cerebrale doorbloeding vergeleken met de normotensieve controles in het laatste trimester van de zwangerschap. Deze toename in was niet gerelateerd aan vasodilatatie van de grote cerebrale vaten want de diameter van deze 4 grote vaten bleef onveranderd. Het is speculatief of deze toename het gevolg is van veranderingen van de downstream resistance, toename van de cardiac output, danwel een toename van de mean arterial pressure, en/of factoren betreffende de locale autoregulatie van het centraal zenuwstelsel.

Hoofdstuk 5 beschrijft de resultaten van diffusie-gewogen MRI bij vrouwen met eclampsie. Deze specifieke techniek faciliteert de differentiatie tussen vasogeen en cytotoxische vormen van cerebraal oedeem. Dit is een belangrijk punt want vasogeen oedeem is reversibel, terwijl cytotoxisch oedeem daarentegen het aanwezig zijn van infarcering suggereert. De studie includeerde 27 opeenvolgende nullipare vrouwen met eclampsie, gedefinieerd als zwangerschapshypertensie samen met een of meerdere grand mal insulten. Alle vrouwen ondergingen T1-gewogen, Fluid-Attenuated Inverse Recovery (FLAIR), alsmede diffusie-gewogen MRI scans binnen de eerste 36 uur na een insult. Bij aanwijzingen voor cytotoxisch oedeem werd na 6 weken de MRI herhaald. Cerebrale infarcering werd gediagnosticeerd wanneer bij follow-up MRI persisterende laesies van de witte stof werden gevonden alsmede aanwijzingen voor cerebrale gliose. Op twee na werd bij alle vrouwen (93 %) reversibel vasogeen oedeem gevonden. Deze laesies werden met name, maar niet exclusief, in de subcorticale witte en aangrenzende grijze stof in de parieto-occipitale gebieden gevonden. Zes vrouwen vertoonden gebieden met cytotoxisch oedeem overeenkomstig cerebrale ischemie. Vijf van deze zes vrouwen had persisterende gebieden van infarcering bij de follow-up studies, hoewel asymtomatisch. Concluderend, het MRI spectrum van cerebrale laesies in eclampsie varieert van initieel reversibel vasogeen oedeem dat kan voortschrijden tot cytotoxisch oedeem en infarcering in bijna 25 % van de vrouwen.

Deze bevindingen bevestigen dat eclampsie, net als andere vormen van hypertensieve encephalopathie, kan optreden terwijl de bloeddruk zich binnen de gebruikelijke marge van intacte cerebrale autoregulatie bevindt en behoud van normale cerebrale bloeddoorstroming gegarandeerd zou moeten zijn. Specifiek, 2/3 van de beschreven vrouwen had een maximale mean arterial pressure van < 120 mmHg.

Hoofdstuk 6 evalueert het effect van magnesium sulfaat op de maternale doorbloeding. Twaalf vrouwen met preeclampsie ondergingen velocity-encoded fase-contrast MRI alvorens en direct na infusie van een 6 gram magnesium sulfaat oplaaddosis. De bloeddoorstroming werd bepaald in de bilaterale proximale arteriae cerebri mediae en posteriores. De studie werd 6 weken postpartum herhaald ter bepaling van de cerebrale doorbloeding in de niet-zwangere conditie. Er werd geen significant verschil gevonden in de diameter noch de cerebrale doorbloeding van de onderzochte cerebrale arteriën voor of na de magnesium sulfaat therapie. In de niet-zwangere situatie werd eveneens geen verschil gevonden in de vaatdiameter en de cerebrale doorbloeding. Concluderend, de afwezigheid van een significant verschil in cerebrale bloeddoorstroming van de arteriae cerebri mediae en posteriores voor en na infusie van een 6 gram $MgSO_4$ oplaaddosis in vrouwen met preeclampsie zet vraagtekens bij de algemeen voorgestelde rol van $MgSO_4$ als een vasodilator van deze arterieen en/of suggereert de afwezigheid van vasoconstrictie van de grote cerebrale vaten in preeclampsie.

Hoofdstuk 7 De pathofysiologie van Reversible Posterior Leukoencephalopathy syndrome (RPLS) een onderwerp is van uitgebreide discussie. Vele onderzoekers zijn van mening dat dit syndroom het resultaat is van het falen van de cerebrale autoregulatie. Hierbij ontstaan er in het hersenparenchym gebieden van zowel geforceerde vasodilatatie en extreme vasoconstrictie, waardoor een toename van de vasculaire permeabiliteit met als gevolg extravasatie van vocht. Zoals beschreven in hoofdstuk 3 worden bij vrouwen met eclampsie opvallende gelijkenissen gevonden met niet-zwangere patiënten met RPLS. Deze bevindingen komen overigens ook overeen met de klassieke histopathologische studies van hersenlaesies in eclampsie, beschreven als (sub-corticaal oedeem, splinterbloedinkjes en infarcering. Tenslotte komen de neuropathologische bevindingen overeen met welke beschreven voor eclampsie. Vergeleken met normotensieve zwangere vrouwen, is bij vrouwen met preeclampsie de cerebrale doorbloeding toegenomen. Deze toename suggereert het hyperperfusie model voor de ontwikkeling van cerebraal oedeem en eclampsie in plaats van een model waarin vasospasme centraal staat. Oorzaken zijn tot nu toe alleen speculatief en omvatten factoren zoals downstream vasodilatatie, een toename van de cardiac output, toegenomen mean arterial pressure, locale factoren

in het centraal zenuwstelsel, danwel andere factoren betreffende de autoregulatie. Bijvoorbeeld, shear stress en veranderingen in ritmische of pulsatiele flow kunnen het vrijkomen van endotheliale vasoactieve factoren moduleren. Prostacycline, nitric oxide of andere modulerende stoffen zoals endothelium-derived relaxing factor of hyperpolarizing factor (EDRF/ EDHF) kunnen allen een rol spelen in het moduleren van de arteriële compliance.

Concluderend, de cerebrovasculaire conditie in preeclampsie lijkt een continuum te zijn welke initieel wordt gekarakteriseerd door een toename van de cerebrale doorbloeding. We stellen voor dat, in geval van een dysfunctie van het cerebrale endotheel, zodra een kritiek punt is bereikt, een reversibele fase van vasogeen oedeem en convulsies kan optreden. Vervolgens, in bijna 25 % van de vrouwen, kan cytotoxisch oedeem ontwikkelen hetgeen kan resulteren in irreversibele gebieden van infarcering en uiteindelijk weefsel verlies. Ondanks dat in het verleden deze infarcering toegeweten is aan vasospasme ten gevolge van cerebrovasculaire overregulatie wordt in dit proefschrift voorgesteld dat juist de ernst van het vasogeen oedeem, in plaats van een afname van de cerebrale perfusie de focale ischemie initieert. Dit wordt geïllustreerd doordat in de studie patiënten alle gebieden met cytotoxisch oedeem waren ingebed in een groter gebied van vasogeen oedeem. In deze studie werd een transitie van reversibel vasogeen oedeem naar irreversibele cerebrale ischemie en infarcering in bijna een kwart van de patiënten gezien. Hopelijk kan toekomstige vooruitgang in de mogelijkheden van de neurologische beeldvormende technieken, specifiek MRI, ons begrip van de etiopathogenese van de neurologische verschijnselen bij preeclampsie bevorderen.

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 phenomonon 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 difusion) 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 abnormalites 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 pregnany 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 bioavailablity of vasoactive mediators such as prostacylin, 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 signifcantly 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 conjuction with cerebral endothelial dysfuntion, 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.

Manuscripts related to hypertensive disease in pregnancy

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About Parkland Memorial Hospital, Dallas

Parkland Memorial hospital, a 1000-bed facility, is the main teaching institution of the University of Texas Southwestern medical School, located in Dallas, Texas. Parkland delivers more babies each year than any other hospital in the USA. In 2003 15,796 babies were delivered. This large number of deliveries provides excellent experience in both the common and rare complications of pregnancy. The obstetric division serves not only Dallas county, but also serves as a referral source for complicated obstetrical cases for a surrounding 30 county area. Several maternity patients are transported by ambulance or care-flight helicopter annually.

Women identified as having a pregnancy complication are appointed to one of several specialty clinics staffed by maternal-fetal faculty and residents staff. Individual clinics, each specialized to manage a specific pregnancy complication meet weekly. These clinics manage problems such as diabetes, multiple gestation, genetic abnormalities, hypertension, infectious disease, preterm labor, and postterm gestation. Maternal-Fetal experts in these areas use data from these clinics for their research efforts. In addition to the specialty clinics, the 30-bed High Risk Pregnancy Unit within Parkland Hospital is dedicated to the care of maternity patients who require hospitalization and treatment for complications such as preterm labor, pregnancy induced hypertension, preterm rupture of membranes, and placenta previa. The in-patient volume on this high-risk ward, over 1000 patients a year, also affords the division an important research resource. Much of this research is made possible by a computerized database, begun in 1982, and managed by the division's own statistician.This same patient data also adds to the understanding of antenatal disorders on a national scale. The division participates currently in several National Institutes of Health Maternal-Fetal research networks.

Within Parkland Hospital are three Labor and Delivery Units that receive patients from a contiguous third trimester obstetric emergency room (triage unit). All of these units function interdependently. From triage, laboring women are transferred to 1 of 3 Labor & Delivery units, each designated to care for a specific level of medical acuity. Our Labor & Delivery unit with the highest acuity level is staffed by faculty and residents; the lower acuity units by faculty, residents, and certified nurse midwives. Generally, multiparous women with uncomplicated pregnancies are triaged to Labor

& Delivery “4-South”. This unit consists of 6 labor and delivery rooms. Nulliparous women with predominantly uncomplicated pregnancy are triaged to Labor and Delivery East which consists of 12 labor and delivery rooms and 2 operating rooms. Both Labor and Delivery “4-South” and “East” are staffed by nurse midwives with supervision of OB/GYN residents and faculty. Most nurse midwives are graduates of the Parkland School of Midwifery. Labor and Delivery West receives complicated pregnancies from the triage unit. Is has 18 labor rooms, 9 delivery/ and operating rooms with a contiguous obstetric recovery room and a 5 bed obstetric critical care unit. Similarly, postpartum recovery care is triaged. Medical staff members provide immediate postpartum care in two obstetrical recovery rooms, each staffed to manage different levels of problem severity. Altogether our Parkland facilities provide a total resource of 30 labor rooms, 8 combined Labor/Delivery/Recovery rooms, 7 delivery rooms, 7 obstetrical operating rooms, a 7-bed obstetrical recovery room and a 5-bed obstetrical critical care unit. Because our obstetrical patients and newborns often require services from other medical specialties, our division has several faculty members who share joint appointments with other departments such as radiology, anesthesiology, and neonatology. These physicians allow us to provide superior patient care and comprehensive medical professional training.

There are a total of 72 obstetrics and gynecology residency positions. This dynamic diverse group of residents physicians comes from different social ethnic geographic and academic backgrounds. Residents spend 4-6 month during each year of training on services which deal with labor and delivery skills, with comprehensive routine obstetrics, with high-risk obstetrics, or with ultrasound and prenatal genetics. Residents have faculty available in house to serve as instructors and consultants around-the-clock. At night, no less than four faculty remain within the hospital for this sole purpose. The obstetric division has a 27-year history of providing Maternal-Fetal Medicine fellowships. Currently accredited to train 6 fellows, the 3-year program offers extensive training in pregnancy complications from the simple to the extreme. Fellows gain experience with ultrasonography, amniocentesis, percutaneous umbilical sampling (PUBS), and operative obstetrical skills. Additionally, fellows spend 18 months of the fellowship involved in research activities directed toward a graduating thesis.

Curriculum Vitae Geertruida Gerda Zeeman

26 april 1967	Geboren te Huizen
1979 -1985	VWO *Het Nieuwe Lyceum* te Hilversum
1985 - 1993	Geneeskunde studie aan de *Vrije Universiteit* te Amsterdam
Januari 1993	Artsexamen
1993	Getrouwd met Olaf Veth
1993 - 1994	Research Fellow Department of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Health Sciences Center, Houston, Texas, USA (Yussof Dawood)
1994 - 1998	Opleiding tot Gynaecoloog, *Baylor College of Medicine*, Houston, Texas, USA (Joe Leigh Simpson)
Januari 1997	Geboorte Floris Sebastian
1999 - 2002	Subspecialisatie opleiding Maternal-Fetal Medicine*, University of Texas Southwestern Medical Center (Parkland Memorial Hospital*, Dallas, Texas, USA (F. Gary Cunningham)
Oktober 1999	Geboorte Julia Isabella
2002 - 2003	MSRC beoordelingsstage *Isala Klinieken*, (Jim van Eyck)
November 2002	Geboorte Olivier Nicholas
2003 – 2004	Perinatoloog, *Isala Klinieken*, Zwolle
2004 – heden	Perinatoloog, *Universitair Medisch Centrum Groningen*

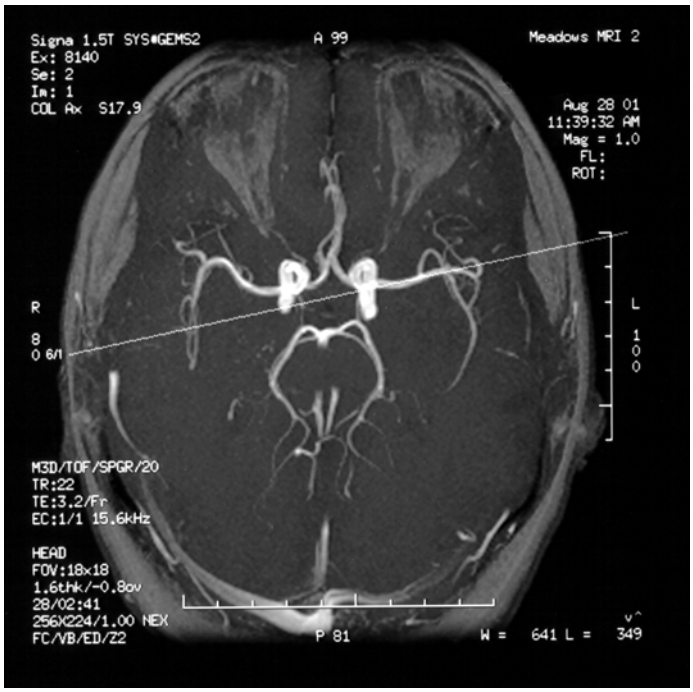

Figure 1. In order to localize the proximal cerebral artery a single transaxial slice (white line) is chosen along the long axis of the middle cerebral artery.

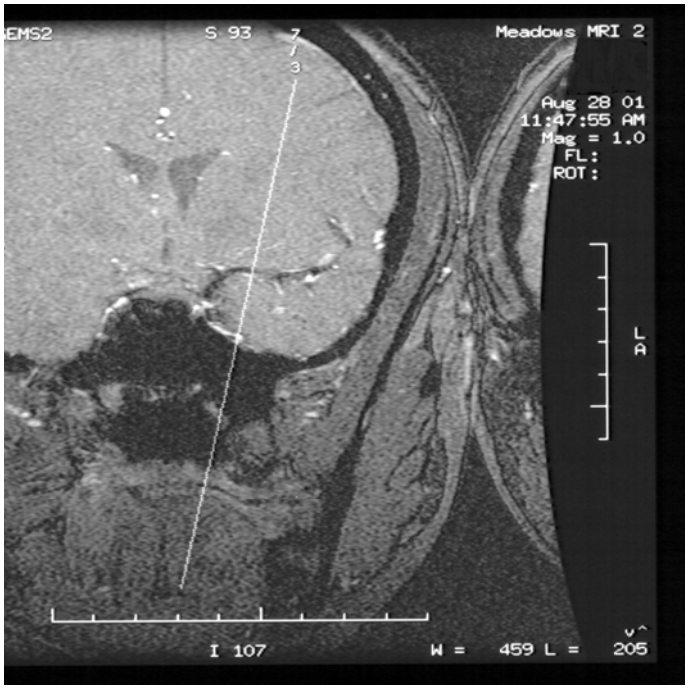

Figure 2. The course of the middle cerebral artery is well defined by this sagittal image allowing placement of a flow image slice perpendicular to a straight section of the artery involved (white line).

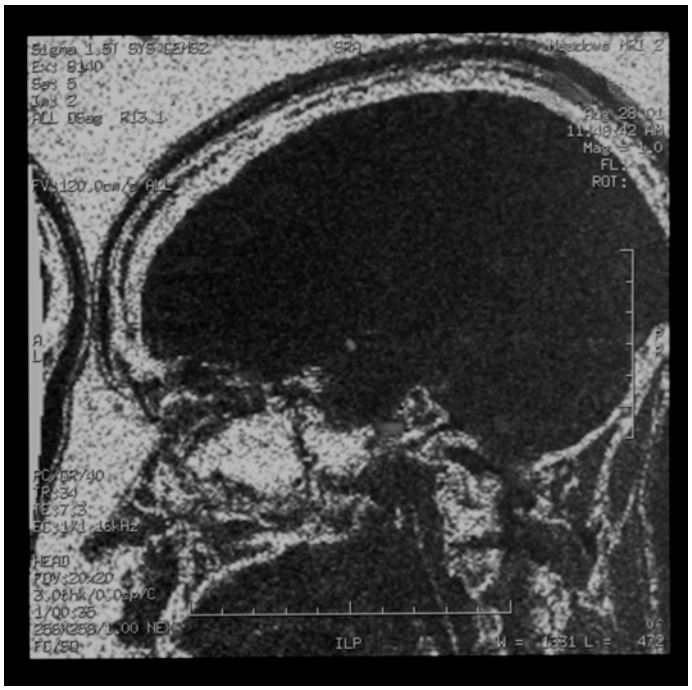

Figure 3. A velocity/area image is obtained with a cross sectional view of the middle cerebral artery (arrow).

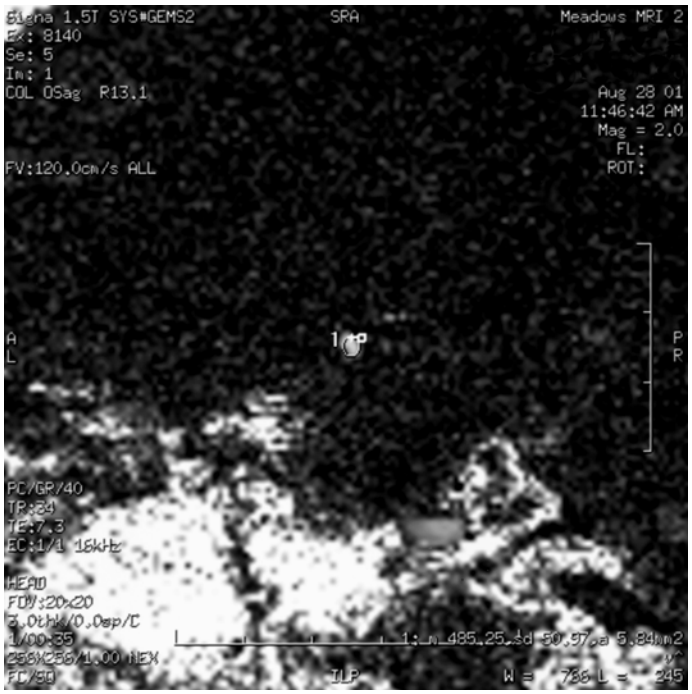

Figure 4. The magnified image demonstrates the region of interest cursors (white circle) around the middle cerebral artery from which area and velocity are calculated.

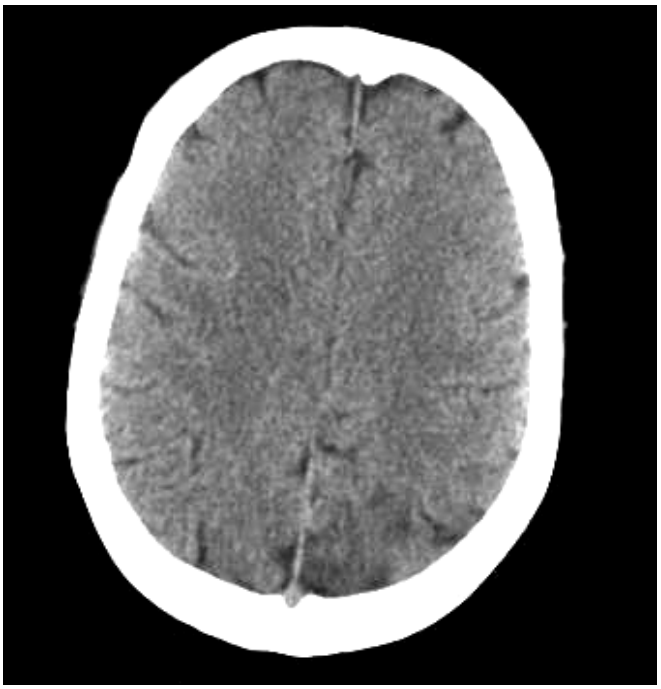

Figure 5. Typical CT appearance of localised low-density areas in the left parieto-occipital lobe consistent with cerebral edema.

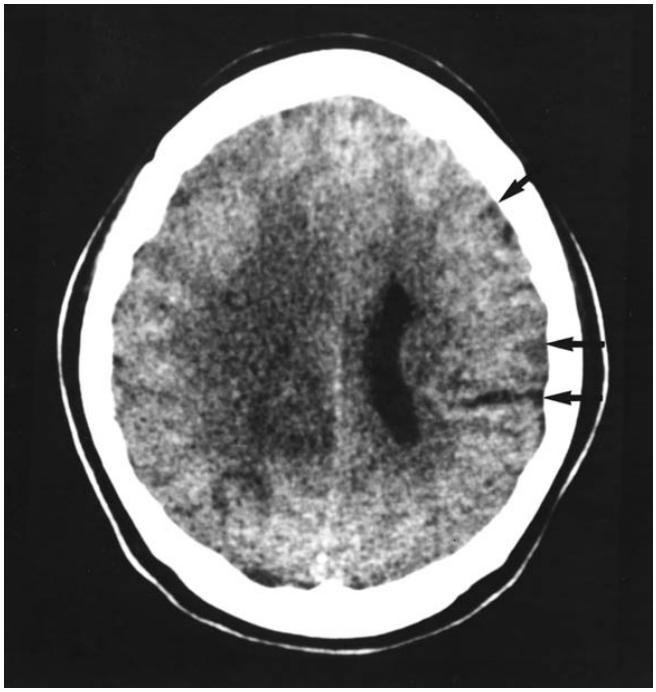

Figure 6. CT appearance of asymmetric cerebral edema. The right ventricle and cerebral sulci are completely effaced whereas the left ventricle is clearly seen with normal appearance of cerebral sulci (arrows)
(With permission from Cunningham [2000])

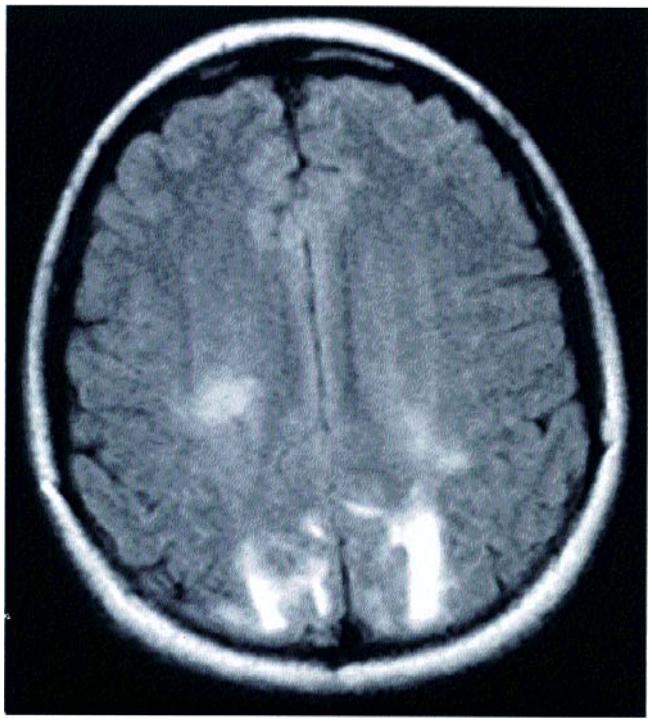

Figure 7. T2 hyperintensity on FLAIR MR images indicate parieto-occipital distribution of vasogenic edema [Zeeman 2004]

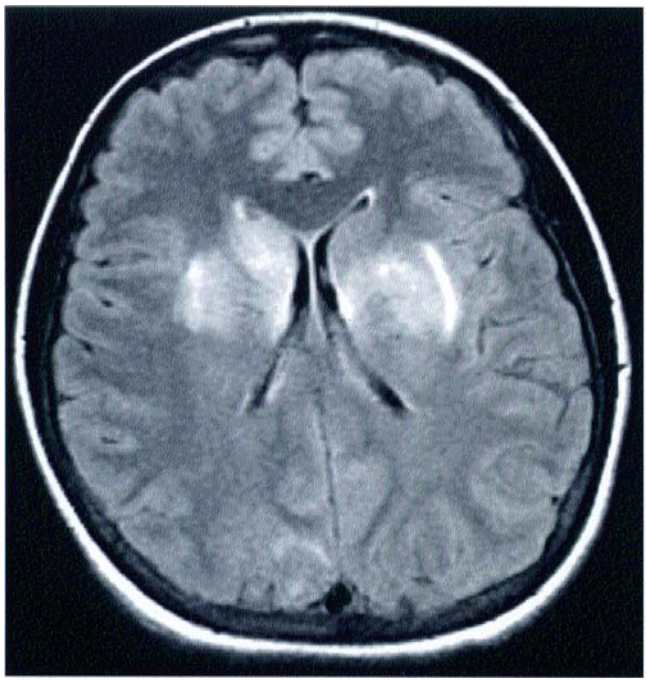

Figure 8. Note on T2-weighted FLAIR image that the predominant changes occur in the basal ganglia regions bilaterally [Zeeman 2004]

Classic pattern of vasogenic edema in eclampsia with associated subcortical infarction

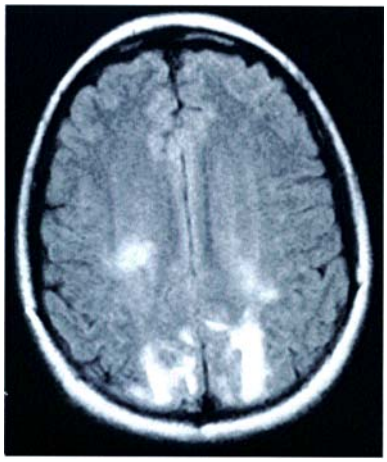

Fig 9.

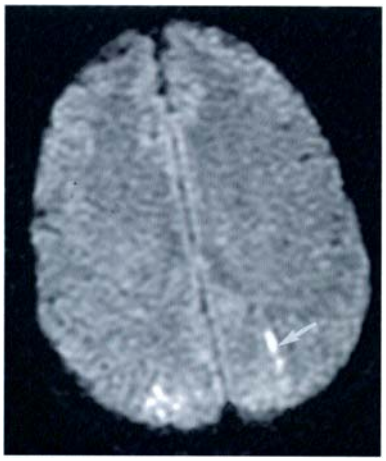

Fig 10.

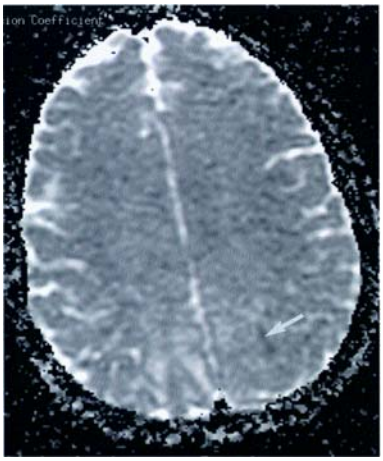

Fig 11.

Figure 9. T2 hyperintensity on FLAIR images indicates parieto-occipital distribution of vasogenic edema.

Figure 10. Within this volume is a smaller area of hyperintensity on DWI (arrow).

Figure 11. This signal is due to restricted diffusion as confirmed by hypointensity on the ADC map (arrow).

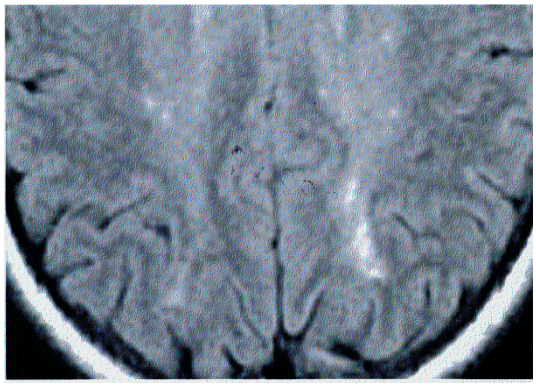

Fig 12.

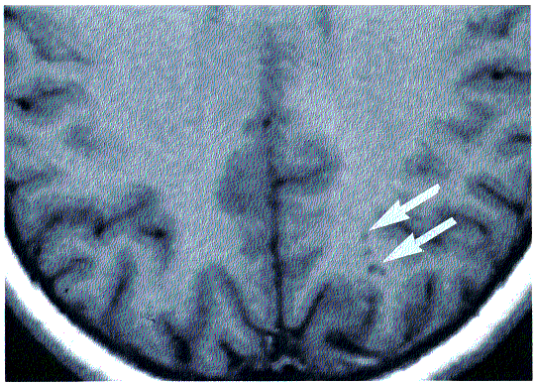

Fig 13.

Figure 12. These findings suggesting areas of subcortical infarction are supported by follow up studies obtained 6 weeks later in which T2 hyperintensity on FLAIR image

Figure 13. Corresponding low signal intensity on T1 weighted image (arrow) indicated evolution to gliosis

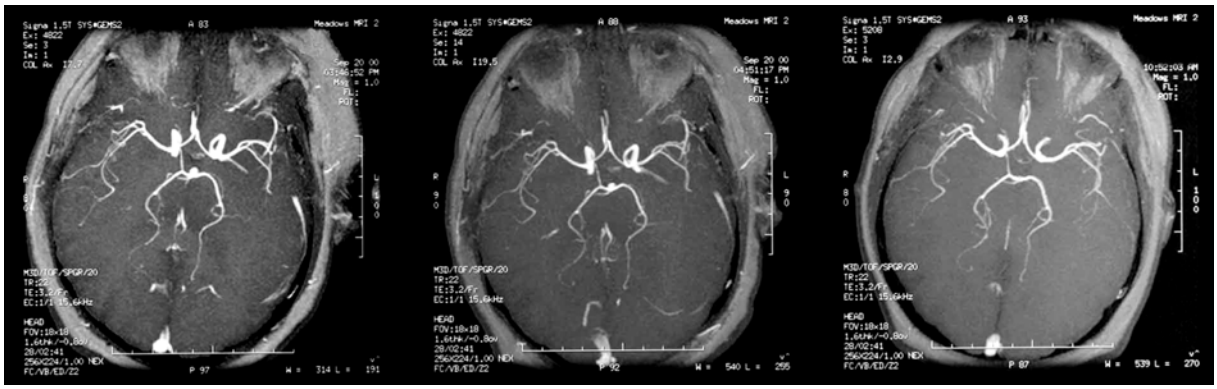

Figure 14. Magnetic resonance angiograms of the same patient before administration of magnesium sulfate (left), immediately after (center) and 6 weeks postpartum (right). No statistically significant change in vessel diameter was noted for bilateral MCAs and PCAs between any of the three studies.