Cerebral hemodynamics in normal and complicated pregnancy

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CHAPTER 9

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES
9.1 Introduction

Advances in measurement techniques and methods have made it possible to study dynamic changes in blood pressure (BP) and cerebral blood flow (CBF), and consequently cerebral autoregulation (CA). In this thesis, these techniques have been applied to normal and complicated pregnancies.

This chapter will provide a summary of the findings in this thesis, followed by a general discussion of (i) the cerebral hemodynamics in normal and complicated pregnancy, (ii) the possibility of predicting preeclampsia, and (iii) perspectives for further research.

9.2 Summary

Previous studies have demonstrated significant changes in cerebral hemodynamics normal pregnancy. Most of these data are derived from the middle cerebral artery, showing decreases in the velocity and resistance index. However, the posterior circulation is believed to be more vulnerable to dysfunctional cerebral autoregulation because of its relative lack of sympathetic innervation, and as an extension of this, eclampsia is sometimes hypothesized to be an expression of the posterior reversible encephalopathy syndrome.

In chapter 2, the effect of gestational age on cerebral blood flow in the anterior and posterior cerebral arteries during normal pregnancy was investigated. A decrease in the anterior cerebral artery (ACA) systolic and mean velocity was found, similar to velocity changes in the middle cerebral artery (MCA), while the diastolic velocity in the posterior cerebral artery (PCA) increased. The common hypothesis is that MCA changes are due to increased vascular distensibility. In both ACA and MCA, RI showed a peak during the second trimester of pregnancy, decreased during the third trimester, then subsequently increased in the postpartum period. The magnitude of the third trimester decrease in RI was smaller for the PCA than for the ACA, which is consistent with the increased diastolic and systolic velocities in the PCA. These results, combined with previously published longitudinal MCA data, show a reduction in velocity in the anterior circulation (MCA and ACA), and an increase in velocity in the posterior circulation (PCA) during normal pregnancy. This might indicate a redistribution of cerebral blood flow from the
anterior territory to the posterior, and may explain the characteristic predominantly posterior brain involvement in women who develop eclampsia.\textsuperscript{5, 6}

These cerebrovascular hemodynamic changes, combined with the systemic cardiovascular changes of pregnancy are remarkable, since the cerebral circulation is dependent on a constant blood supply and is relatively intolerant to increases or decreases in blood volume. The physiological process by which the cerebral blood flow is maintained at an optimal level despite changes in blood pressure is called cerebral autoregulation. \textbf{Chapter 3} describes increased cerebral autoregulation functionality in the second half of pregnancy, as indicated by the autoregulation index (ARI), when compared to non-pregnant women of reproductive age.

Unlike the velocity changes seen in the cerebral arteries, the cerebral autoregulation did not change with gestational age. The autoregulation index is significantly higher in pregnancy, even after controlling for end-tidal CO\textsubscript{2}, but the timing of when this occurs remains unclear since only women after 20 weeks of gestation were included.

In \textbf{chapter 4}, the autoregulation index of normotensive pregnant women was compared with patients with preeclampsia who were studied prior to receiving treatment.

The cerebrovascular complications seen in preeclampsia have been hypothesized to be due to impaired cerebral autoregulation. This may explain the development of eclampsia or other cerebral complications that may occur without sudden or excessive elevation in blood pressure. We demonstrated that the autoregulation index was indeed significantly reduced in preeclamptic women. Although there was no correlation between the ARI and blood pressure, the three patients with the lowest autoregulation index scores (ARI <3) all had chronic hypertension with superimposed preeclampsia requiring two or more antihypertensive agents to control their BP. In addition to changes in the autoregulation index, we also found statistically significant differences in resistance index, pulsatility index, resistance-area product, and cerebral perfusion pressure. Women with superimposed preeclampsia were shown to have a reduced autoregulation index when compared to those with new onset preeclampsia. \textbf{(chapter 6)}, but the autoregulation index in new onset preeclampsia was still lower than that seen in
the control group. Gestational hypertension (GHTN), which is also characterized by new-onset hypertension (but without proteinuria) was not associated with changes in the autoregulation index.

In chapter 5, cerebrovascular hemodynamics in preeclamptic women and normotensive controls were further studied by evaluating the cerebrovascular response to breath holding. Deep breath holding is associated with complex chemical ($\text{PaCO}_2$), mechanical (changes in blood pressure and heart rate), and neural (autonomic nervous system) consequences, all of which affect cerebral blood flow. Cerebral blood flow velocity (CBFV) changes were broken down into standardized subcomponents describing the relative contributions of blood pressure, cerebrovascular resistance index (CVRi), critical closing pressure (CrCP), and resistance area product (RAP). The area under the curve (AUC) was then calculated for changes in relation to baseline values. While the increase in CBF velocity and end-tidal $\text{CO}_2$ was similar in both groups, the AUC for CVRi and RAP during breath holding was significantly different between the groups, indicating an early, transient increase in CVRi and RAP in the control group, which was absent in preeclampsia. Blood pressure had an equal contribution in both groups. We hypothesize that this difference is due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in women with preeclampsia. The reduced vasoconstrictor response may be similar to what has been described in acute stroke patients. Because the subcomponent peak of CrCP was equal in the groups, our study suggests that the metabolic pathway is intact, at least during the relatively small demand of a short breath hold.

Some chronic conditions, including hypertension, diabetes and obesity, are known to increase the risk of developing preeclampsia. The cerebral autoregulation of these were studied in Chapter 6 and 7.

In chapter 7 the impact of diabetes and obesity on cerebral autoregulation in pregnancy was assessed. Diabetes and obesity are not only risk factors for the development of preeclampsia, but also for cardiovascular complications, both of which are associated with endothelial dysfunction. Based on the increased risks for developing preeclampsia and cerebrovascular complications in patients with pregestational diabetes type 2 (DM2), but a less pronounced relationship with gestational diabetes (GDM), we hypothesized that the cerebral
autoregulation is impaired in DM2, but not in GDM. However, the autoregulation index in pregnant women with either diabetes or overweight, was not significantly different to that in healthy pregnant controls. Furthermore, there were no differences in the autoregulation index between women with diet or medication controlled gestational diabetes or DM2. It has to be noted that none of the study participants were known to have microvascular complications or autonomic neuropathy, which are thought to be associated with cerebral autoregulation impairment in DM. Also, all participants had excellent glycemic control (as shown by daily glucose monitoring). Therefore, relatively mild hyperglycemia and short disease duration likely allow for preserved cerebral autoregulation. These findings suggest that if such women are at an increased risk for preeclampsia based on their diabetic and/or high BMI status, it is unlikely to be associated with significant impairment in dynamic cerebral autoregulation prior to the development of the hypertensive state.

Women with chronic hypertension have an increased risk of developing super-imposed preeclampsia, and the risk for cerebrovascular complications during pregnancy is increased with all hypertensive disorders, but is most pronounced with severe preeclampsia and super-imposed preeclampsia. As with diabetes and obesity, these complications are believed to be caused by impaired cerebral autoregulation. In chapter 6 it was shown that the autoregulation index is significantly reduced in CHTN. There was no difference in autoregulation index between women with CHTN who were using antihypertensive medication versus those who were not.

In chapter 6 and 8, we investigated whether analysis of the different components of cerebral hemodynamics can identify those pregnant women who are destined to develop preeclampsia. While the development or progression of the disorder cannot be prevented, identification of women at risk will aid in early diagnosis and appropriate management, and may improve maternal and perinatal outcome.8

In chapter 6, a prospective cohort study was performed to study the autoregulation index in normotensive and hypertensive pregnancy. Seven patients (23%) with CHTN, 3 patients (10%) in the control group, and 5 patients (25%) with GHTN were studied who
subsequently developed preeclampsia, and were compared to patients who did not develop preeclampsia. The autoregulation index of women with CHTN who subsequently experienced preeclampsia was lower compared with those who did not. This was not true for women with GHTN or control subjects who later experienced preeclampsia.

In chapter 8, the cerebral hemodynamics of the MCA in 405 low-risk women in the second trimester of pregnancy were studied. MCA velocity, resistance index (RI), pulsatility index (PI) and cerebral perfusion pressure (CPP) were evaluated as potential predictors for the future development of preeclampsia. Seven (1.7%) subjects subsequently did develop preeclampsia. RI and PI values were lower in these seven women. Other measurements and derived values describing cerebrovascular flow and resistance were not significantly different at the time of measurement, but mean systemic blood pressure was higher. An RI of < 0.54 and a PI of < 0.81 were clinically useful in predicting subsequent preeclampsia. Areas under the receiver–operating characteristic curves for RI and PI were 0.93 and 0.93, respectively, with optimal sensitivity and specificity of 86% and 93% for both variables. Positive and negative likelihood ratios were 11.8/0.15 (RI) and 12.3/0.15 (PI). These data suggest that transcranial Doppler indices of low MCA resistance in the second trimester are predictive of the subsequent development of preeclampsia.

9.3 General discussion

9.3.1 Cerebral hemodynamics in pregnancy

While the systemic circulation undergoes extensive changes during pregnancy, the brain is dependent on a constant blood supply, and relative intolerance to increases or decreases in blood volume. Previous studies have shown a decrease in blood flow velocity (transcranial Doppler) or blood flow (MRI) in the middle cerebral artery (MCA).\textsuperscript{1, 9, 10}

The MCA is the largest of the cerebral arteries and supplies most of the cerebral hemisphere and deep subcortical structures, but the posterior cerebral artery (PCA) is believed to be more vulnerable to dysfunctional cerebral autoregulation in preeclampsia.\textsuperscript{3} In chapter 2, a decrease in the anterior cerebral artery (ACA) systolic and mean
velocity during normal pregnancy was described, similar to the velocity changes in the MCA.\textsuperscript{1} The diastolic velocity in the PCA, however, increased.\textsuperscript{11} This suggests that during normal pregnancy, there may be some degree of redistribution of cerebral blood flow from the MCA and ACA territory to that of the PCA. This redistribution may explain the vulnerability of the posterior circulation.\textsuperscript{5, 6} Several studies, predominantly performed in animals, have shown attenuated sympathetic innervation of the posterior cerebral circulation (vertebrobasilar arteries) when compared with the anterior circulation (MCA and ACA, arising from internal carotid arteries),\textsuperscript{3} and less effective autoregulation during pregnancy.\textsuperscript{12}

In chapter 3, enhanced cerebral autoregulation functionality was shown in the second half of pregnancy, when compared to non-pregnant fertile women. This improved autoregulation was independent of gestational age, and remained significant even after controlling for end-tidal \textit{CO}\textsubscript{2} (Et\textit{CO}\textsubscript{2}).\textsuperscript{13} This is in accordance with previous studies in both human\textsuperscript{14} and rats.\textsuperscript{15, 16}

The alterations seen in cerebral hemodynamics during pregnancy might be caused by a combination of changes in carbon dioxide, hormones, cytokines, and other circulating factors,\textsuperscript{12} as well as changes in perivascular innervation.\textsuperscript{17} The individual differences between the anterior and posterior circulations, as regards to their specific adaptations to pregnancy may reflect a variable sensitivity of these vessels to these changes.

The pregnant state is characterized by respiratory alkalosis and hypocapnia. A decrease in \textit{PaCO}\textsubscript{2} is known to cause physiologic vasoconstriction, increased cerebrovascular resistance and decreased cerebral blood flow velocity due to constriction of the small arteries.\textsuperscript{18, 19} This also leads to an improved autoregulatory capacity.\textsuperscript{20}

However, as said, the autoregulatory functionality (ARI) was significantly higher in pregnancy, even after controlling for Et\textit{CO}\textsubscript{2}. Furthermore, the resistance index (RI), often interpreted as an indicator of cerebrovascular resistance, decreased in the second half of pregnancy in both ACA and PCA, while the blood flow velocity increased in the PCA and decreased in the ACA. These results may indicate that \textit{PaCO}\textsubscript{2} is not a main determinant of cerebrovascular changes in pregnancy, and/or that the relationship between RI and
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Cerebrovascular impedance is more complex. The lower cerebrovascular resistance in pregnant rats has been explained by outward remodeling of parenchymal arterioles and increased capillary density coupled with the physiologic hemodilution seen in pregnancy.¹⁷

During pregnancy, estrogen levels rise until term. Estrogens have a vasodilatory effect on the microvasculature²¹ through endothelial nitric oxide (NO) synthase.²² Indeed, cerebral blood flow declines with he onset of menopause and increases with hormone replacement therapy.²³, ²⁴ By studying the effect of ovarian suppression and stimulation, a significant correlation between increased estrogen levels and increased blood flow velocity in the internal carotid artery has been shown together with a concomitant decrease in cerebrovascular resistance.²⁵ In chapter 3 it was demonstrated that RI decreased during pregnancy in both the ACA and the PCA and increased postpartum. Cipolla et al. have shown gestation-induced changes in endothelial and neuronal nitric oxide synthase¹⁷ in Sprague-Dawley rats and significantly decreased nitric oxide synthase expression in their anterior versus posterior cerebral cortex.¹² Such regional differences might explain the different slopes seen in the study described in chapter 3. However, studies evaluating the role of NO on the human cerebral autoregulation are sparse, and have shown conflicting results, reporting impaired autoregulation following NO inhibition,²⁶ and no effect²⁷.

Other factors that might be involved in the enhancement of autoregulatory capacity could be the renin-angiotensin system (RAAS),²⁸ the perivascular innervation, vascular structure or cytokines, all known to be altered in preeclampsia.¹⁷

Better understanding of the factors affecting cerebral hemodynamics in normal pregnancy might help shed light on the pathophysiology of complications seen in hypertensive pregnancies. The timing of changes during pregnancy and postpartum and the mechanism by which pregnancy enhances cerebral autoregulation functionality have yet to be explored.

9.3.2 Cerebral autoregulation in hypertensive pregnancy

The cerebrovascular complications seen in preeclampsia have been hypothesized to be caused by impaired cerebral autoregulation.
This may explain the seemingly insidious development of eclampsia or other cerebral complications without sudden, or excessive elevation in blood pressure.

**Chapter 4 and 6** showed that cerebral autoregulation is indeed impaired in pregnant women with preeclampsia and even more in superimposed preeclampsia.\(^\text{29, 30}\) Interestingly, there was no correlation between the autoregulatory index (ARI) and blood pressure, and impaired autoregulation could not be identified based on clinical symptoms such as headache or visual disturbances. However, the largest degree of impairment was found in women with superimposed preeclampsia who required two or more antihypertensive drugs to control their blood pressure.\(^\text{30}\) Furthermore, the functionality of autoregulation (ARI) is impaired in pregnant women with chronic hypertension, and especially in those with chronic hypertension who subsequently experienced superimposed preeclampsia when compared with women who did not progress to preeclampsia.\(^\text{29}\) The ARI of patients with new onset preeclampsia was not much different from the ARI of patients with chronic hypertension\(^\text{29}\) and the ARI of women with gestational hypertension was similar to those with normotensive pregnancy.

The spectrum of conditions (which ranged from superimposed preeclampsia, preeclampsia, and chronic hypertension to gestational hypertension and control subjects), along with their associated spectrum in ARI, might reflect a range of endothelial impairment. Although preeclampsia is defined by hypertension and proteinuria, it involves multiple organ systems (e.g. renal, liver, brain, vascular, coagulation, placenta) that may lead to different pathophysiological phenotypes. These phenotypes, combined with the heterogeneity in disease severity may explain the large range seen in ARI in preeclampsia.

Previous studies suggest that altered expression of angiogenic factors produces systemic endothelial dysfunction and plays an important role in the pathogenesis of preeclampsia.\(^\text{31}\) The extent of these deviations depends on the type of hypertensive disorder, being more pronounced in preeclampsia than in women with chronic and gestational hypertension when compared with control subjects.\(^\text{32-34}\) Another study found an altered angiogenic balance in preeclampsia,
but not in gestational hypertension. The proteinuria that is seen in preeclampsia is caused by renal endothelial dysfunction and is also suggested to be related to this angiogenic imbalance. These results are in agreement with the findings in chapter 6 – i.e. lowest ARI in the preeclampsia group and similar ARI in women with gestational hypertension and control group.

In addition to ARI, resistance area product (RAP) and critical closing pressure (CrCP) were also studied in chapter 6. Women with gestational hypertension and preeclampsia were found to have a higher RAP - which is thought to reflect myogenic activity - but decreased CrCP - indicative of metabolic control, which counteracts the effect of RAP and suggests an abnormal neurovascular coupling. These changes were not seen in patients with chronic hypertension. Previous studies using transcranial Doppler have also shown an impaired response to CO₂ inhalation in patients with preeclampsia, but not with chronic hypertension.

A difference in cerebrovascular response to a breath holding challenge between normotensive controls and patients with preeclampsia was also seen (chapter 5). In addition to influencing PaCO₂, deep breath holding also affects the sympathetic nervous system via the diving reflex, resulting in changes in cerebral blood flow velocity (CBFV), blood pressure and cerebrovascular resistance (represented by either the cerebrovascular resistance index (CVRI) or combined CrCP and RAP). Although the CBFV and blood pressure responses were similar in both groups, patients with preeclampsia lacked a transient increase in both CVRI and RAP during the initial phase of the breath holding maneuver. We hypothesized that this was due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in women with preeclampsia. The similar subcomponent peak of CrCP between the groups suggests that the metabolic pathway during the relatively small demand of a short breath hold is intact.

While it now seems evident that cerebral hemodynamics are affected by preeclampsia, the timing of these changes and the impact of neurological, laboratory or degree of endothelial dysfunction are not known. Much more future research is needed to elucidate these factors.
9.3.3 Cerebral autoregulation in pregnancies complicated by diabetes, obesity and chronic hypertension

Women with chronic hypertension, pre-pregnancy diabetes mellitus (DM2), and obesity have a substantially increased risk of preeclampsia compared with women without such risk factors. The association between preeclampsia and gestational diabetes is less pronounced.\textsuperscript{41, 42} This inconsistency is likely to be due to heterogeneity of the population with gestational diabetes, with regard to the degree of impaired glucose metabolism, glycemic control, and its time of onset during pregnancy. Further confounding the association is that women with gestational diabetes often have co-existing obesity, which in itself is an independent risk factor for preeclampsia.\textsuperscript{43, 44}

The mechanisms by which these conditions increase preeclampsia risk are largely unknown, but these risk factors are associated with underlying maternal endothelial dysfunction. The latter might also affect the cerebral autoregulation and may increase susceptibility of the vasculature to the hemodynamic changes in pregnancy.\textsuperscript{31} Indeed, these women develop preeclampsia in smaller increments of angiogenic factor dysregulation.\textsuperscript{31, 34} This angiogenic dysregulation is thought to produce systemic endothelial dysfunction and to be responsible for the clinical manifestations of preeclampsia.\textsuperscript{31}

\textbf{Chapter 7} showed that cerebral autoregulation is not impaired in women with (uncomplicated and non-vasculopathic) diabetes in pregnancy. Furthermore, the functionality of autoregulation (ARI) is equally effective in euglycemic women with and without prepregnancy obesity.\textsuperscript{45}

Other studies on cerebral autoregulation in non-pregnant patients with type 2 diabetes mellitus have shown conflicting results, with both normal autoregulation\textsuperscript{46, 47} and affected dynamic autoregulation with\textsuperscript{48} and without\textsuperscript{48, 49} the presence of microvascular disease. However, comparison with these studies is difficult due to differences in age, disease duration and severity, and gender. None of the patients studied in \textbf{chapter 7} had microvascular complications or autonomic neuropathy, both of which are thought to be associated with impairment of cerebral autoregulation in diabetes.\textsuperscript{47, 50} In pregnancy, these factors (characterized by baseline proteinuria and the stage of the disease according to the White classification) are associated with
the development of preeclampsia. None of the women studied in chapter 7 had baseline proteinuria or class D diabetes or higher which might explain the lack of impaired autoregulation. Furthermore, interpretation of previous studies on gestational diabetes and adverse pregnancy outcomes has been complicated by the fact that these studies were not differentiated according to disease severity. In chapter 7 both diet- and medication controlled gestational diabetes were studied separately, but there was no difference in autoregulation in either of these sub groups. As in the patients with type 2 diabetes in chapter 7, we hypothesized that the excellent glycemic control (as shown by daily glucose monitoring), relatively mild hyperglycemia and short disease duration allow for preserved cerebral autoregulation. Another explanation for the absence of impaired autoregulation might be pregnancy in and of itself, since pregnancy, as described above, has been shown to enhance autoregulation. Lastly, in chapter 7 autoregulation was only studied within the context of spontaneous fluctuations in blood pressure during rest, which is mainly a myogenic activity. Therefore, the possibility of cerebral blood flow changes induced by metabolic activity such as might be present in patients with impaired PaCO\textsubscript{2} cerebrovascular reactivity can not be excluded.

The findings in chapter 7 suggest that the increased risk for preeclampsia in patients with (pre-)gestational diabetes and/or overweight is unlikely to be associated with significant impairment in dynamic cerebral autoregulation prior to the development of the hypertensive state. Whether this holds true for patients with advanced diabetic complications remains to be determined.

In contrast to what is seen in diabetes and overweight status, chronic hypertension, which is also associated with maternal endothelial dysfunction, does in fact affect cerebral autoregulation in pregnancy (chapter 6). Women with chronic hypertension had a significantly decreased autoregulation index (ARI) when compared to normotensive controls. This was even true after excluding those women who subsequently developed superimposed preeclampsia. These results may explain the reason why women with chronic hypertension or preeclampsia have an increased risk for developing cerebral complications such as stroke during pregnancy, even without sudden or excessive elevation in blood pressure.
The cerebral autoregulation in pregnancies complicated by chronic hypertension is discussed in more detail in the following section.

9.3.4 Prediction of preeclampsia

Although there is no proven effective method for the prevention of preeclampsia, identifying women at risk would allow individually tailored antenatal care and early delivery if needed, thereby reducing the risk of developing severe complications.

Previous studies have used different risk factors including clinical history, complete blood count and biochemical markers to predict preeclampsia, with conflicting results.\textsuperscript{8, 33, 54} The cerebral hemodynamics have been studied in normotensive and hypertensive pregnancy by using transcranial Doppler ultrasound and velocity-encoded phase-contrast magnetic resonance imaging (MRI).\textsuperscript{55, 56}

Chapter 8 suggests that transcranial Doppler indices of low resistance in the middle cerebral artery in the second trimester are predictive of the subsequent development of preeclampsia in a low-risk, ethnically homogeneous population.\textsuperscript{57} This supports previous studies showing a reduced resistance index and/or pulsatility index either before\textsuperscript{58} or after\textsuperscript{59-61} the clinical development of preeclampsia. The results are also consistent with studies that show preeclampsia to be characterized by a hyperdynamic state with elevated cardiac output and reduced peripheral resistance early in pregnancy.\textsuperscript{62, 63} The patients studied in chapter 8 who developed preeclampsia all had a relatively mild and late-onset disease. This supports the suggestion of Valensise \textit{et al.}\textsuperscript{64} that women likely to develop early-onset preeclampsia (< 34 weeks) show elevated peripheral vascular resistance before the onset of hypertension and proteinuria, while those who will develop preeclampsia late in pregnancy have an initially low vascular resistance.\textsuperscript{64} The results in chapter 8 are consistent with this proposal: six of seven preeclamptic patients were diagnosed at or after 34 weeks’ gestation.

Chapter 6 evaluates the cerebral autoregulation in hypertensive disorders of pregnancy (superimposed preeclampsia, preeclampsia, chronic hypertension and gestational hypertension vs. controls), including a subgroup analysis of women who did or did not develop preeclampsia. Resistance and pulsatility indices were indeed decreased
in women with chronic hypertension who subsequently developed superimposed preeclampsia (data not shown). This was not the case for women with chronic hypertension who did not progress to superimposed preeclampsia or the control group. Only three women in the control group (10%) developed preeclampsia, and one of them developed early onset preeclampsia (gestational age 31+6 weeks). She did in fact demonstrate increased pulsatility and resistance indices.

Riskin-Mashiah et al.\textsuperscript{58} also showed that decreased cerebral resistance indices predicted the subsequent development of preeclampsia. However, two cerebral autoregulatory challenge tests at the time of examination (CO\textsubscript{2} inhalation and hand grip), showed a normal vasodilatory response, suggesting intact autoregulation.\textsuperscript{58} Chapter 6 demonstrates that the autoregulation index of normotensive women was not predictive of the development of preeclampsia.\textsuperscript{29} Janzarik et al.\textsuperscript{14} also did not find impairment of cerebral autoregulation as an early feature of preeclampsia.

In light of the angiogenic dysregulation prior to the clinical presentation of preeclampsia it is now suggested that the cerebrovascular resistance changes prior to the development of preeclampsia does not represent cerebrovascular dysfunction, but rather a physiologic compensatory response.

As was true for normotensive women, women with gestational hypertension who did or did not progress to preeclampsia had similar autoregulation indices (ARIs). However, women with chronic hypertension who subsequently experienced preeclampsia had lower ARIs compared with those who did not. Their ARI was comparable to patients who already had superimposed preeclampsia. There are two possible explanations for this finding. First, the changes in cerebral autoregulation may occur prior to the manifestations of clinical symptoms of superimposed preeclampsia, reflecting early manifestation of disease or the underlying pathophysiology. This is further supported by the finding that chronic hypertension outside of pregnancy does not appear to alter cerebral autoregulation, even in sustained untreated middle-aged and older people.\textsuperscript{65-67} In addition, lower MCA resistance in low risk pregnant women in the second trimester, who likely lacked endothelial dysfunction at the time of examination, predicted the development of PE.\textsuperscript{57} These findings, together with evidence that angio-
genic factors have been detected in maternal serum 5 to 10 weeks prior to the onset of preeclampsia, suggest that ARI may indeed be impaired in these cases well before the clinical manifestation of disease.\textsuperscript{31, 32, 35} If this is in fact true, ARI can potentially be used as a screening tool.

A second explanation may be that reduced ARI is indicative of baseline endothelial dysfunction, making pregnant women with chronic hypertension more susceptible for developing superimposed preeclampsia. This is supported by the finding that women with chronic hypertension or diabetes develop preeclampsia at a lower level of angiogenic disturbance,\textsuperscript{33} and would also explain why the ARI in women with gestational hypertension and controls was normal. To take this a step further, in chronic hypertension, endothelial function is already impaired while the angiogenic imbalance may cause a second hit and the clinical manifestation of superimposed preeclampsia. This theory is in agreement with Noori \textit{et al.}, who found impaired endothelial function in the brachial artery prior to the alteration of angiogenic factors.\textsuperscript{35}

Even though this theory is attractive, the study in \textit{chapter 6} was not designed to determine whether autoregulation index can be used as a predictor for preeclampsia, and results should therefore be interpreted with caution. Whether the lower ARI is due to preexistent differences or early affected cerebral circulation in pregnant women with chronic hypertension remains to be determined.

The two studies in low risk women in \textit{chapters 6 and 8} show a striking difference in the incidence of preeclampsia. In chapter 8, only 7 out of the 405 women studied (1.7\%) developed preeclampsia.\textsuperscript{57} In the other study, 10\% developed preeclampsia (3/30).\textsuperscript{29} The specific characteristics of the populations studied might explain this difference. The first one was conducted in a low-risk, middle-class, almost exclusively Caucasian population (92\%), with a very low regional incidence of preeclampsia. In the second study only 43\% of the control group was of Caucasian ethnicity and participating women had a higher pre-pregnancy BMI. Information on the socioeconomic status of the women in this study is unfortunately not available. Both ethnicity and pre-pregnancy BMI are known to be independently associated with the development of preeclampsia and can, at least partly, explain this difference in incidence of preeclampsia.
9.3.4 Final conclusions

1. Normal pregnancy causes a redistribution of the cerebral blood flow from the anterior to the posterior circulation. This redistribution may explain why the posterior circulation is most vulnerable to cerebrovascular complications in preeclampsia and eclampsia.

2. Cerebral autoregulation functionality of the middle cerebral artery is enhanced in the second half of normal pregnancy, and is independent of gestational age. This remains true even after controlling for end-tidal CO2, which is physiologically lower in pregnancy.

3. Cerebral autoregulation functionality (ARI) is impaired in preeclampsia and even more so in superimposed preeclampsia. There is no correlation between the autoregulatory index and blood pressure. This may explain the development of eclampsia or other cerebral complications without sudden, or excessive elevation in blood pressure.

4. Women with preeclampsia show a difference in cerebrovascular response in the initial phase of a breath holding maneuver. This might be due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in preeclampsia, while the metabolic pathway during this relatively small demand of a short breath hold appears to be intact.

5. Cerebral autoregulation is impaired in women with chronic hypertension, and especially in those with chronic hypertension who subsequently experienced superimposed preeclampsia when compared with women who did not progress to superimposed preeclampsia.

6. Cerebral autoregulation is not impaired in gestational hypertension, well-controlled (pre-)gestational diabetes or in overweight women.
7. Indices of low middle cerebral artery resistance as derived by transcranial Doppler in the second trimester are predictive of the subsequent development of preeclampsia in a low-risk, ethnically homogeneous population.

8. The cerebral autoregulation in women with normal blood pressure and with gestational hypertension is similar for those who do and do not progress to preeclampsia. However, this functionality of women with chronic hypertension who subsequently experience superimposed preeclampsia is lower compared with those who do not.

9.3.5 Future perspectives

1. The details of how pregnancy affects cerebral blood flow and cerebral autoregulation is largely unknown. Better understanding of the factors affecting cerebral hemodynamics in normal pregnancy might help understand the pathophysiology of complications seen in hypertensive pregnancies. The timing of changes during pregnancy and postpartum and the mechanisms by which pregnancy enhances cerebral autoregulation functionality have yet to be explored. This should preferably be studied using longitudinal studies with measurements before, during, and after pregnancy.

2. In this thesis, the middle cerebral artery was predominantly studied, but the posterior cerebral artery is believed to be more vulnerable to dysfunctional cerebral autoregulation in preeclampsia. Future research should focus on the posterior circulation in normal pregnancy and preeclampsia.

3. It seems evident that cerebral hemodynamics are affected by preeclampsia, and some of the possible cofounders were studied in the different chapters. However, increasing the statistical power of studies, might provide a more consistent picture of what is happening when considering all co-factors included.
4. The timing of the changes in the cerebral hemodynamics seen in patients with preeclampsia and the impact of neurological, laboratory or the degree of endothelial dysfunction are not known. Future research is needed to elucidate these factors. Patients with severe preeclampsia are treated with magnesium sulfate for seizure prophylaxis while the specific mechanisms of action remain unclear. Previous studies using transcranial Doppler have shown changes in cerebral hemodynamics after administration of magnesium sulfate and future studies should elaborate on this.

5. Cerebral autoregulation assessed in the middle cerebral artery was shown to be impaired in women with chronic hypertension who subsequently experienced superimposed preeclampsia well before the clinical manifestation of disease. A prospective longitudinal study including pregnant women with chronic hypertension should be performed to further elucidate this and evaluate the possibility of using autoregulation as a screening tool.
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