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Eclampsia & preeclampsia

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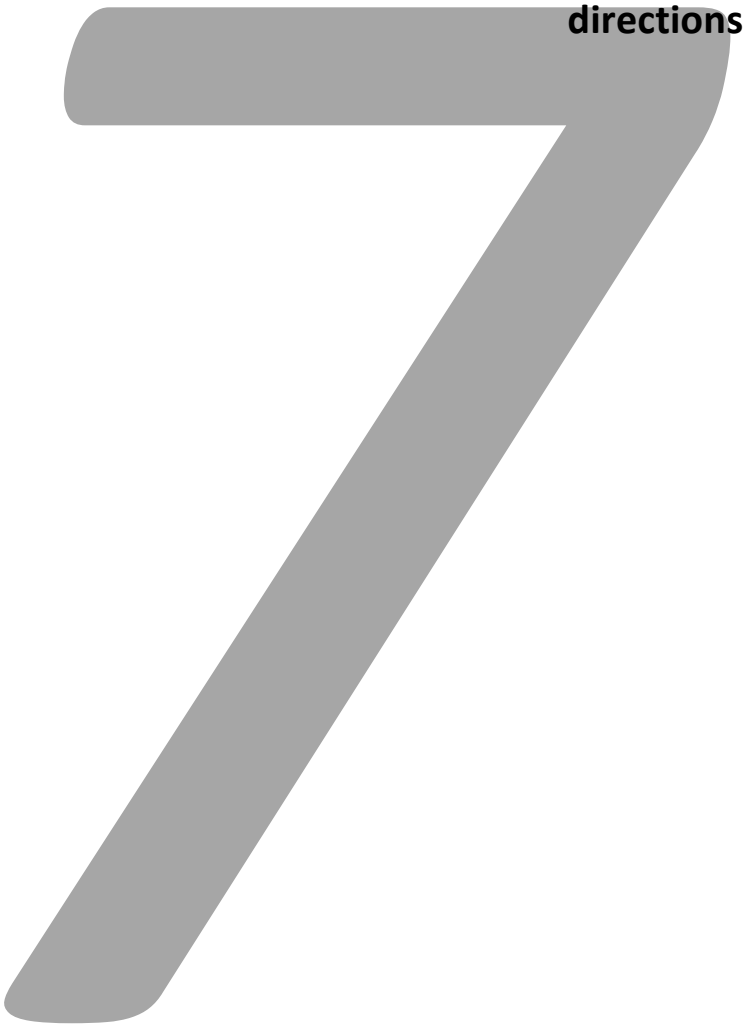
Summary, general discussion, conclusions and future directions



Summary

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Summary

In the **first part** of this thesis the long-term consequences of eclampsia and preeclampsia on the maternal brain are presented. This part describes the result of MR imaging and cognitive testing in women several years after pregnancies that were complicated by eclampsia or preeclampsia.

In **Chapter 2** outcome of the Cognitive Failures Questionnaire (CFQ) in 30 formerly eclamptic, 31 formerly preeclamptic and 30 healthy parous control women were compared. The scores on this test were significantly worse in the group of women who had had a pregnancy complicated by eclampsia (43.5 ± 14.6) compared to control women (36.1 ± 13.9), p = 0.049. Formerly preeclamptic women had a similar score to control women but this was not significantly different from the formerly eclamptic women (36.9 ± 13.9). The more seizures formerly eclamptic women had suffered, the worse their score on the CFQ. The women who had experienced more than two eclamptic seizures scored 60.0 ± 14.5 versus 39.1 ± 10.9 in the women who suffered a single seizure (p = 0.005). The CFQ is a subjective test; the participant answers questions about memory and concentration. Therefore, the outcome of this study only signifies an indication of the cognitive functioning of these women in daily life. However, the fact that women with multiple seizures reported most cognitive impairment seems to be an indication that eclamptic seizures may have long-term sequelae and are more harmful than was previously thought. In **Chapter 3** more data are presented to support this hypothesis. Thirty-nine formerly eclamptic women underwent MR imaging on average 7 years after the index pregnancy. Twenty-nine healthy parous control women, on average 5 years after the index pregnancy, were matched for age and elapsed time since the index pregnancy and also underwent MR imaging. We found that 41% of the formerly eclamptic women had white matter lesions on the MRI scans, while this was the case in 17% of the control women (p = 0.03). The volume of the white matter lesions was significantly larger in the formerly eclamptic group (0.041 mL ± 0.016) compared to the control group (0.004 mL ± 0.002, p = 0.025). With increasing number of eclamptic seizures the prevalence and severity of white matter lesions increased (test for trend for prevalence p = 0.009, Kruskal-Wallis for volume p = 0.042). Together, these findings suggest that the paradigm that eclamptic women fully recover after eclamptic seizures, provided that haemorrhage does not occur, should be revised. The prevention of seizures by administering magnesium sulphate should be emphasized in this regard. In **Chapter 4** the presence and volume of

cerebral white matter lesions in 73 formerly preeclamptic women and 75 healthy parous control women was assessed. Of the formerly preeclamptic women 37% had white matter lesions on MR imaging, which was a significantly more compared with 21% of the control women ($p = 0.036$). Formerly preeclamptic women also had more severe lesions (volume-index: 0.11 ± 0.33 mL) compared with the controls (0.015 ± 0.04 mL, $p = 0.019$). The white matter lesions were not related to neurologic symptoms at the time of pregnancy, the concomitant presence of HELLP syndrome, magnesium sulphate administration or diastolic blood pressure > 110 mmHg at the acute moment. Preeclampsia with an onset and delivery prior to 37 weeks was associated with increased prevalence and severity of cerebral white matter lesions. Formerly preeclamptic women who were currently hypertensive were associated with presence of white matter lesions. Presence of current hypertension, absolute current blood pressure values and current weight were significantly higher in the formerly preeclamptic group. Retrospectively, it was impossible to determine which women had posterior reversible encephalopathy syndrome (PRES) during their preeclamptic pregnancy, simply because in general such women do not undergo cerebral imaging. Therefore, in our group we can only suggest contribution of cerebral edema to the development of white matter lesions, but we are unable to proof this. Recent data have emerged to indicate that women with a history of preeclampsia are predisposed to develop cardiovascular disease later in life, including stroke. The white matter lesions found in our study could be an early expression of cardiovascular disease manifesting it self as cerebrovascular disease. Most vulnerable are women who suffered early onset (<37 weeks) preeclampsia. Emphasis should be placed on ameliorating risk factors of cardiovascular disease in this young group of women.

In the **second part** of this thesis animal studies are presented that give insight in the cerebral vasculature during pregnancy and hypertension.

In **Chapter 5** a rat model of hypertensive encephalopathy was used to mimic eclampsia. Two groups of nonpregnant (n = 8 in both groups) and two groups of late-pregnant (n = 8 in high salt, n = 9 in low salt group) Dahl salt-sensitive rats were fed either a high salt containing diet (8% NaCl) or a low salt containing diet (<0.7% NaCl). After two weeks of this diet, for the pregnant animals at the end of gestation, their posterior cerebral arteries were used to determine the effects of hypertension and pregnancy on the reactivity and remodeling of pial arteries. We found that pregnancy prevented hypertensive remodeling because there were no structural differences between cerebral arteries from the hypertensive and normotensive pregnant rats, while remodeling was present in the nonpregnant hypertensive animals. Also, the passive and active diameters were similar in

both pregnant groups. At higher pressures there was diminished myogenic reactivity in pregnant animals regardless of hypertension, suggesting that pregnancy makes the brain more susceptible to loss of autoregulation when blood pressure increases. Since this was also found in a previous study where animals were made hypertensive with a nitric oxide synthase inhibitor, we concluded that the lack of remodeling and the diminished myogenic reactivity is an effect of pregnancy independent of the method by which hypertension was induced. In this study, we also stained perivascular nerves of the posterior cerebral arteries with a pan-neuronal stain. We found that in the presence of hypertension perivascular innervation was significantly decreased, while during pregnancy the nerve density was significantly increased regardless of the presence of hypertension. The type of perivascular nerves could not be distinguished due to the use of a pan-neuronal stain and the cause and consequence of the changes remained unclear. Therefore, in **Chapter 6** we investigated the posterior cerebral arteries of nonpregnant (n = 23), late-pregnant (n = 22), post partum (n = 23) and male (n = 22) Sprague Dawley rats. We determined the nerve density in the posterior cerebral arteries not only with a pan-neuronal stain; we also measured the nerve density of sympathetic (tyrosine hydroxilase) and trigeminal (calcitonin gene-related peptide, CGRP) perivascular nerves. In this rat strain the total perivascular nerve density was unchanged during pregnancy, probably due to genetic differences. The sympathetic nerve density was similar in all groups, but the trigeminal nerve density increased during pregnancy and was significantly higher compared to the male animals. The sensitivity to CGRP was not altered by pregnancy or gender, neither was the reactivity to norepinephrine. The significance of the increased CGRP-containing perivascular nerves of cerebral arteries in the pregnant animals is unclear, but in this chapter we speculate about its importance in pain signalling and cerebral hyperperfusion. Especially in migraine, a disease that shares features with eclampsia and in which CGRP is known to play a major role.

General discussion

The causes of eclampsia.

A classic thought is that a patient with mild preeclampsia progresses through a phase of severe preeclampsia and eventually develops eclampsia. It appears, however, that a significant number of eclamptic women never reach blood pressures generally considered to be hypertensive prior to developing tonic-clonic seizures. This appears similar for non-obstetric patients who develop PRES.[1] We raised the question whether pregnancy in and

of itself could cause a left shift of the cerebral autoregulation curve which would make the brain susceptible to loss of autoregulation at lower blood pressures. Two studies from our lab have shown that isolated posterior cerebral arteries from pregnant rats have diminished myogenic reactivity at increasing pressure independent of hypertension.[2,3] This may indicate a left shift of the autoregulation curve, however isolated arteries lack several factors that influence the cerebral autoregulation such as perivascular innervation. In vivo experiments indicated that the blood pressure at which autoregulation breakthrough occurred did not differ between pregnant and nonpregnant animals [4], which contradicts the hypothesis of a pregnancy-induced left shift of the autoregulation curve. The brains of these pregnant animals, however, did contain more edema after cerebral autoregulation breakthrough in comparison to nonpregnant animals, especially in the posterior part of the brain.[4] This suggests that the blood-brain barrier is more susceptible to disruption in pregnancy. Pregnancy prevents hypertensive remodeling of posterior cerebral arteries in rats [2,5] and even reverses remodeling that is present in chronically hypertensive rats.[6] In addition, penetrating arterioles undergo outward remodeling during pregnancy.[7] This may contribute to increased wall stress and failure of the usual protective mechanisms for the downstream vasculature in case of acute hypertension and cause subsequent vulnerability of the blood-brain barrier. Posterior cerebral arteries from late pregnant rats demonstrate increased permeability of the blood-brain barrier as indicated by increased endocytosis and paracellular transport when hydrostatic pressure is increased and when forced dilatation occurs [8,9], but pregnancy does not appear to alter mRNA expression of key tight junctions.[7]

The primary site of blood-brain barrier disruption in acute hypertension is the cerebral veins.[10] During acute hypertension cerebral venular pressure increases and the blood-brain barrier becomes leaky in venules and veins.[11] Cerebral veins from virgin female rats have an increased hydraulic conductivity when they are exposed to plasma from pregnant women compared to normal physiologic salt solution.[12] In addition, when veins were exposed to plasma from women with early onset preeclampsia, hydraulic conductivity is increased significantly in comparison to exposure to plasma from normotensive pregnant women. There was no difference in myogenic activity or vascular tone in posterior cerebral arteries between normal pregnant plasma and preeclamptic plasma.[12] It seems therefore that an important factor in the development of cerebral vasogenic edema during pregnancy and in eclampsia, is the vulnerability of the blood-brain barrier.

What causes vulnerability of the blood-brain barrier during pregnancy or during (pre)eclampsia? In pregnant rats cerebral vascular resistance is more severely decreased and cerebral blood flow more severely increased compared to nonpregnant rats during

acute hypertension.[7] Together with an increase in capillary density in the posterior part of the brain[7] and outward remodeling of penetrating arteries, it may well be that the blood-brain barrier is more susceptible to breakthrough during acute hypertension because of relatively increased hydrostatic pressure and cerebral blood flow. Furthermore, in the pregnant cerebral vasculature vascular endothelial growth factor (VEGF) appears to play a role, although it is not the only factor that influences the blood-brain barrier.[12] In experiments on traumatic brain injury, ischemia/reperfusion or infection several factors play a role in the regulation of blood-brain permeability.[11] Examples of these factors are bradykinin, histamine, nitric oxide and cytokines such as tumor necrosis factor, VEGF and interleukins. In addition, oxidative stress influences the permeability of the blood-brain barrier.[13] Endothelial dysfunction, oxidative stress and pro-inflammatory cytokines are known to be important in the pathophysiology of preeclampsia [14,15] and PRES [16] and it is reasonable to suggest that some of these factors are associated with increased permeability of the blood-brain barrier in this patient category.

Whether or not there is a pregnancy-related change of the cerebral autoregulation curve is an important question. Based on the experimental data mentioned above, it seems that pregnancy may cause a modest left shift of the curve and a greater increase in cerebral blood flow when blood pressure increases compared to nonpregnant state which make the brain more susceptible to autoregulatory breakthrough. In addition, circulating factors and endothelial dysfunction in preeclampsia cause vulnerability of the blood-brain barrier resulting in formation of vasogenic edema even at relatively low blood pressures. Much more future research in both humans and animal models is needed to elucidate the adaptations of the cerebral autoregulation curve in pregnancy and in (pre)eclampsia. Once the main factors responsible for this vulnerability have been identified, focus should be on the development of blood-brain barrier protecting agents.

The long term consequences of eclampsia and preeclampsia on the maternal brain.

The brain after eclampsia.

Several years after a pregnancy complicated by severe preeclampsia, a large group of women complain about suboptimal physical and mental well being.[17] A high percentage of such women complain about recurrent headache, visual disturbances, fatigue, decreased concentration and mental problems.[17] Most often, no pathological substrate is found in these women to explain their complaints. The incidence of post-traumatic stress disorder is also increased in formerly preeclamptic women.[18,19] In Chapter 2 we found that several years after eclampsia women report to perform worse in daily life with regard to cognitive

function compared to healthy parous controls, whereas formerly preeclamptic women had the same score as controls on this subjective test. Objective neurocognitive tests in formerly preeclamptic women show conflicting results.[20-22] Brussé et al. showed that formerly severe preeclamptic women have impaired short and long term memory [20], Baecke et al. found mental slowing and affected working memory after preeclampsia but no impaired concentration or self-reported cognition [21], while Postma et al. found no difference in executive function and sustained attention between formerly preeclamptic women and healthy parous controls.[22] The number of participants in all of these studies is relatively small, however, the findings suggest that there is a clear correlation between mental well being and a history of preeclampsia but that cognitive functioning after preeclampsia may not be largely impaired. In formerly eclamptic women however, the number of seizures is related to both self-reported cognitive impairment and decreased sustained attention.[22,23] The incidence of post-traumatic stress disorder following eclampsia is unknown, but these findings suggest that there may be a difference in etiology of the reported impaired cognitive function between preeclampsia and eclampsia. Although there are no studies on cognitive functioning following an episode of PRES in non-obstetric patient categories, it seems likely that vasogenic edema and/or the seizures during an episode of PRES in eclampsia can explain the impaired cognitive functioning several years later. In Chapter 3 we found that the prevalence and volume of white matter lesions in the brains of young women several years after eclampsia were higher compared to healthy parous control women. The prevalence and severity increased linearly with the number of seizures, comparable to the findings of decreasing cognitive function and sustained attention with increasing number of seizures.[22,23] This strengthens our hypothesis of the relationship between PRES and subsequent impaired cognitive functioning.

What is the pathogenesis of the white matter lesions that we found in formerly eclamptic women? A plausible scenario, that has been suggested before in humans [24,25] and in animal studies [26], is that cerebral vasogenic edema develops to such an extent that cerebral microvasculature is compressed in the narrow space of the skull. This leads to hypoxia, ischemia and eventually to microinfarction. The fact that the burden of lesions increases with increasing severity of eclampsia, supports this theory. On the other hand, the seizure activity in and of it self may cause neuron damage to the brain, since patients with epilepsy also have a high incidence of white matter lesions.[27,28] Alternatively, women who experience eclampsia may well be predisposed to develop brain white matter lesions in later life independent of the eclamptic seizures. One way or the other, it appears that eclamptic seizures are more harmful to the maternal brain than was previously thought. Eclampsia is not a one-time event of which the patient can expect full clinical recovery.

Therefore, it should be emphasized that prevention of eclamptic seizures and prevention of recurrence of seizures is very important. This can be established by magnesium sulphate administration as has been shown in the Magpie trail.[29] In addition, serious attention should be paid to symptoms of post-traumatic stress disorder in women following a pregnancy complicated by preeclampsia, eclampsia and HELLP syndrome.

The brain after preeclampsia.

Not only women with a history of eclampsia (i.e. with a history of PRES) demonstrate an increased prevalence of white matter lesions. Also formerly preeclamptic women do. To what degree the presence of PRES contributed to the subsequent development of white matter lesions in formerly preeclamptic women, is unknown, because MR imaging was not performed at the acute moment of preeclampsia and the women who may have had imaging features of PRES could obviously not be identified retrospectively. Significantly more formerly preeclamptic women were currently hypertensive and the presence of white matter lesions was associated with current hypertension. The presence and development of white matter lesions in middle-aged and older adults are associated with vascular risks and there is a strong correlation between white matter lesions and hypertension in particular.[30,31] It is therefore possible that the development of white matter lesions in formerly preeclamptic women is initiated by two factors which may be independent from each other: PRES and/or the increased cardiovascular risk in this patient group. There is solid epidemiologic evidence that the risk for cardiovascular events later in life is increased after a preeclamptic pregnancy.[32] The risk of fatal and non-fatal coronary heart disease, hypertension, stroke and venous thromboembolism is significantly increased. Early-onset preeclampsia (<37 weeks) is associated with an even greater risk of future cardiovascular disease. Several years after a preeclamptic pregnancy, markers for cardiovascular disease are increased, especially in women with early onset preeclampsia.[33-36] Although the exact underlying mechanism of the increased risk for cardiovascular disease following a pregnancy complicated by preeclampsia remains unknown, preeclampsia and atherosclerosis share risk factors such as chronic hypertension, dislipidemia, obesity, metabolic syndrome and insulin resistance. A current concept is that pregnancy is a vascular and metabolic 'stress test' for a woman's health later in life.[33,37] She carries a modest risk of cardiovascular disease prior to pregnancy and when she becomes pregnant, this is a scenario of metabolic and vascular stress. She develops preeclampsia because she 'fails' to adapt to the cardiovascular and metabolic challenges of pregnancy. This is associated with an increased risk of cardiovascular disease and cardiovascular events will become manifest at an earlier age compared to women

with an uncomplicated pregnancy. It may well be that the white matter lesions that we found in our formerly preeclamptic women did not necessarily develop during their pregnancy. It is possible that because of their constitutional cardiovascular make-up these women develop preeclampsia during pregnancy and, independently, cerebrovascular lesions - in this case white matter lesions - later in life. In this scheme, early-onset preeclampsia differs from late-onset preeclampsia in that it carries a higher risk. That early-onset and late-onset preeclampsia are different entities has been suggested by others.[38,39] Recently, it has become apparent that postpartum lifestyle intervention improves several risk factors for cardiovascular disease in women with a history of preeclampsia, intra uterine growth restriction or gestational hypertension.[40] In this study weight, hip-circumference, waist-circumference, total cholesterol, LDL cholesterol, HDL cholesterol and heart rate decreased significantly. Blood pressure and fasting glucose and insulin levels did not significantly change.[40] This is a very interesting and important finding which provides an opportunity to develop lifestyle intervention programs for women with a history of preeclampsia in order to establish primary prevention of cardiovascular events.

White matter lesions in young cohorts of women

In the elderly population the prevalence and volume of white matter lesions are correlated with development of cognitive impairment, stroke and dementia.[41] Therefore, it is tempting to immediately conclude that the white matter lesions found in our cohorts will lead to cognitive impairment, stroke and dementia. However, currently it is unknown how the white matter lesions in our young (average 38 years) cohorts will develop over time. In formerly preeclamptic women the risk of stroke later in life is increased [42], however, it is unknown which of these women had white matter lesions prior to stroke. The correlation between dementia and a history of preeclampsia has not been demonstrated either, although the preeclampsia STOX1 gene is upregulated in preeclamptic placentas and also in brain tissue of late-onset Alzheimer's disease patients.[43] Long term follow up studies (20 – 30 years) of cognitive function and cerebral imaging would provide insight in the relationship between white matter lesions and (pre)eclampsia earlier in life and neurodegenerative or cerebrovascular disease later in life.

Conclusions

1. Eclampsia is not a one-time event of which a woman can expect to recover undoubtedly if she survives and the seizures are not complicated by cerebral hemorrhage. Each seizure may carry a risk for cerebral damage and increasing impairment of cognitive function.

2. The importance of preventing eclamptic seizures and prevention of recurrence of seizures in an eclamptic patient should be emphasized.

3. The prevalence and severity of cerebral white matter lesions is increased in women with a history of (pre)eclampsia and with an average age of 38 years. The prevalence and severity of these lesions is most pronounced in preeclamptic women who delivered before 37 weeks of gestation.

4. Formerly eclamptic and formerly early-onset preeclamptic women are particularly vulnerable with regard to the long-term consequences on the maternal brain. Since these consequences are probably vascular in origin and because these women are known to be predisposed to develop cardiovascular and cerebrovascular disease later in life, early and frequent follow-up of cardiovascular risk factors is warranted post partum.

5. In animal models pregnancy prevents hypertensive remodeling in posterior cerebral arteries. Pregnancy also diminishes myogenic reactivity at higher transmural pressures in these arteries, independently of the presence of hypertension. These findings suggest increased vulnerability of the cerebral vasculature during pregnancy, which predisposes to the blood-brain barrier disruption when blood pressure increases acutely.

6. Cerebral perivascular innervation is altered by pregnancy. Which type of nerves are subject of alteration (sympathetic, parasympathetic or trigeminal) seems to be dependent on rat or animal species. In Sprague-Dawley rats pregnancy has a trophic effect on CGRP-containing trigeminal nerves, but because this is not accompanied by altered myogenic reactivity of posterior cerebral artiers to CGRP, there is no changed influence on cerebral blood flow regulation. Possibly, the increased trigeminal

perivascular innervation is related to nociception. However, how pregnancy alters the cerebral perivascular innervation, is largely unknown. How changes on perivascular innervation during pregnancy influence the cerebral blood flow and permeability of the blood-brain barrier, especially during acute hypertension, has yet to be discovered.

Future perspectives

1. How pregnancy affects cerebral blood flow, cerebral autoregulation, the blood-brain barrier and cerebral perivascular innervation is currently largely unknown. Studies in animals are needed to create insight in the physiologic adaptations of the cerebral vasculature during pregnancy. In addition, these physiologic adaptations should be compared to the possible maladaptation in animal models of (pre)eclampsia. Furthermore, experiments in higher order animal species should be done to relate more easily to human subjects.

2. How and why the blood-brain barrier disrupts in eclampsia/PRES at relatively low blood pressures, especially at the posterior region of the brain, has yet to be elucidated. The identification of markers for blood-brain barrier disruption in serum or cerebrospinal fluid such as S100B, other neuroinflammatory markers or free hemoglobin deserves further interest. In addition, different levels of the cerebral vasculature should be investigated because only very few data on cerebral veins and penetrating arterioles during pregnancy and concomitant acute hypertension are currently available.

3. The long-term consequences of PRES in non-obstetric patients should be investigated. By including non-obstetric patients, larger cohorts can be studied and more insight can be generated on the pathophysiology of long-term consequences after PRES, both dependent and independent of the underlying disease that causes PRES. In addition, by including non-obstetric PRES patients, more insight can be generated on the underlying pathophysiology of the development of PRES, in other words; what makes the brain vulnerable to blood-brain barrier disruption and edema formation?

4. Objective neurocognitive studies are warranted to better evaluate the cognitive function of formerly eclamptic women. The outcomes of these studies should preferably be linked to neuroimaging findings such as structural MRI, diffusion tensor imaging or fMRI. In addition to neurocognitive testing, other long-term consequences of eclampsia should be ruled out such as visual impairment based on cortical lesions.

5. The cohorts that we studied in this thesis represent a group of young women. Future research should be performed to monitor the development of white matter lesions

during life in this group of patients. Who are the women that develop severe cognitive impairment, dementia and stroke later in life with relation to presence and severity of white matter lesions at a younger age?

6. Since lifestyle intervention has been shown to be effective on several markers for cardiovascular disease shortly after preeclampsia, emphasis should be on prevention of cardiovascular disease with diet, supplements, exercise and treatment of risk factors such as hypertension and diabetes mellitus. Within this group, the women with early-onset preeclampsia should be monitored and coached most intensively considering the high risk they have in comparison to those women who experienced late-onset preeclampsia. Additional research is needed to determine treatment options for women with a history of eclampsia who may complain of suboptimal neurocognitive functioning.

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