The effect of pre-eclampsia on retinal microvascular caliber at delivery and post-partum

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Abstract

Background

Pre-eclampsia is a pregnancy specific disorder characterised by new-onset hypertension after 20 weeks gestation. The disease contributes to gross maternal vascular dysfunction of which endothelial dysfunction, resulting in increased peripheral resistance, is a key component. Women with a history of pre-eclampsia are more likely to develop long-term hypertension and cardiovascular disease. The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, retinal image analysis.

Aims and objectives

The aim of this study was to compare the retinal vessel caliber at delivery and 1-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

Methods

This was a case-control study of women who had pre-eclampsia and controls, performed at a tertiary referral Hospital in Pretoria, South Africa. The study group comprised of 40 women with severe pre-eclampsia and 40 normotensive women with uncomplicated pregnancies. Macula–centred digital photos of the eye were taken at delivery and 1-year post-partum. Retinal vessels were analysed and summarised as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE). The CRAE and CRVE were corrected for mean arterial blood pressure to produce the corrected central retinal arteriolar equivalent (cCRAE) and corrected central retinal venular equivalent (cCRVE).

Results

The cCRAE and cCRVE were significantly lower in the pre-eclamptic group when compared to the control group both at delivery and 1-year post-partum (p < 0.001). Although there

was some increase in the cCRAE and cCRVE between delivery and 1-year in the pre-eclamptic group and control groups, these increases were not significant.

Conclusion

Retinal artery and venular caliber changes that occur during pregnancies affected by pre-eclampsia persist for up to 1 year post-partum. These changes may reflect a permanent, long-term microvascular dysfunction and may be useful as a biomarker of future vascular risk.

Keywords: Retinal microvascular calibre, pre-eclampsia, hypertension

Introduction

Pre-eclampsia is a pregnancy specific disorder characterised by new onset hypertension after 20 weeks gestation. Although the pathogenesis of pre-eclampsia is still poorly understood, it is well recognised that the disease contributes to gross maternal vascular dysfunction.[1] Endothelial dysfunction, resulting in increased peripheral resistance, is an integral part of the maternal syndrome. The ischemic placenta releases a number of pro- and anti-angiogenic factors and inflammatory markers into the maternal circulation. These factors are critical in mediating vascular function.[2] Vessels of women with pre-eclampsia show hypersensitivity to vasopressors and decreased response to vasodilators and vascular levels of vasodilators such as nitric oxide and prostacyclin are reduced in women with pre-eclampsia.[2,3,4,5,6]

The degree of dilatation and constriction of the retinal microvasculature during normal pregnancy have been shown to correlate with the physiological changes in the mean arterial blood pressure.[7] Differences in retinal microvasculature are believed to reflect cerebrovascular changes and are associated with systemic changes in vascular response.[8] The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, image analysis.[8] Retinal imaging primarily measures retinal microvessel caliber and retinal vessel caliber is relatively stable in healthy individuals with only subtle constriction for each decade increase in age.[9]

Lupton et al compared the changes in retinal microvessel caliber during pregnancy between women who had a normotensive pregnancy to those who subsequently developed pre-eclampsia.[10] The central retinal arteriolar equivalent corrected for mean blood pressure (cCRAE) was significantly lower at term in the pre-eclamptic group compared to women who were normotensive during pregnancy. In general populations, such narrowing of retinal arteriolar caliber has been associated with increased risk of severe hypertension and stroke.[11,12] However it is uncertain whether changes in retinal arteriolar vessel caliber during pregnancies complicated by pre-eclampsia recover after delivery of the fetus and placenta or persist beyond the immediate post-partum period and whether such changes may be

markers of future risk. There have been studies showing that women with a history of pre-eclampsia are more likely to develop hypertension and cardiovascular disease in later life.[13,14]

The aim of this study was to compare the retinal vessel caliber at delivery and 1-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

Methods

This was a case-control study of women with severe pre-eclampsia at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria South Africa, from 1 April 2013 – 30 March 2016. This study formed part of a larger study of pre-eclamptic women which included the evaluation of cardiac diastolic function using echocardiography and the investigation for the presence of cerebral white matter lesions (WMLs) by magnetic resonance imaging (MRI). Recruitment of patients took place from 1 April 2013 – 30 March 2015 and follow-up visits took place from 1 April 2014 – 30 March 2016. Post-partum women (day 2-7 post-delivery) with severe pre-eclampsia were identified every morning during the labour ward round. Women were informed of the study if they were fit to be transported to various departments in the hospital for imaging studies. Retinal images were collected at delivery and 1 year post-partum in patients who also consented to undergoing echocardiography and MRI imaging at delivery and were agreeable to follow-up visits. Normotensive women who had uncomplicated pregnancies served as the control group. Hypertensive disorders were classified according to the classification and diagnosis of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[15]

Retinal imaging was performed using the Topcon TRC-NW8 45^{0} non-mydriatic retinal fundus camera. Photographs were taken between day 2-7 post-delivery and at 1 year post-partum. Women were rested for a few minutes in a dark room before photography to achieve pupil dilatation without pharmacological mydriasis. Macula-centred digital photographs of both fundi were taken. The right eye was chosen for analysis because retinal vessel characteristics are comparable between the right and left eyes.[16] Photographs were graded at the Singapore Eye Research Institute. Retinal image graders were blinded to the clinical information of the study patients. Images were graded using a semi-automated retinal vascular caliber measurement software program which identified all retinal vessels that passed through an area between ½ and 1 disc diameter from the optic disc margin (zone B) (Figure 1) and measured the caliber of the arterioles and venules.[17] Retinal vascular caliber was assessed using a standardised protocol based on the revised Knudtson-Parr-Hubbard formula.[18] Retinal arteriolar and venular calibers were summarised using the 6 largest arterioles and the 6 largest venules as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively.

Figure 1. Digitized retinal photograph. Zone B is a half-disc to one and half disc diameter from the optic disc margin. Retinal vessel diameter measurements were performed in Zone B.
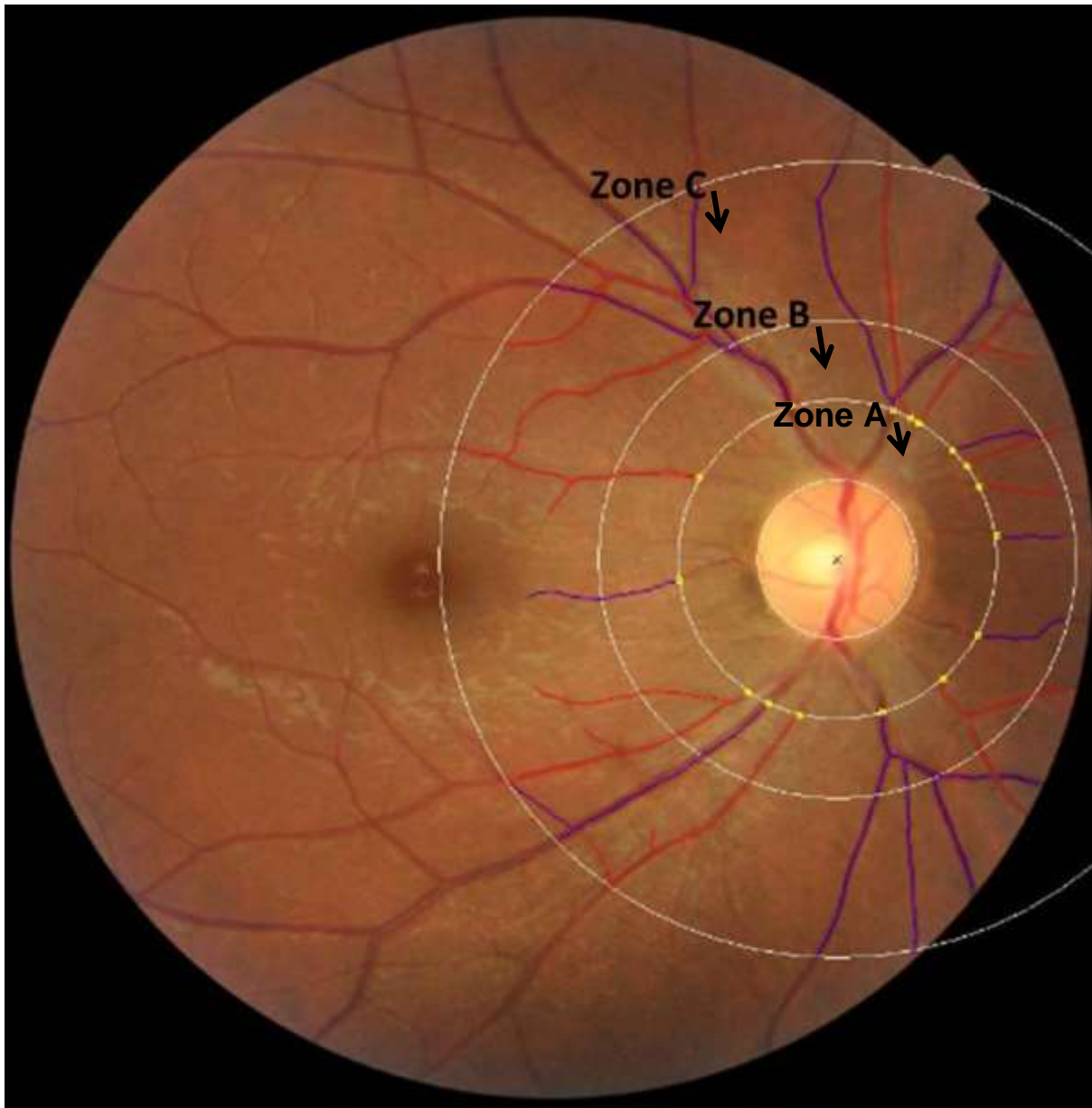
The mean arterial blood pressure (MAP) was calculated using the formula $MAP=DP+1/3(SP-DP)$, where DP and SP represent systolic and diastolic blood pressure respectively. The effect of blood pressure on retinal vessel calibre was corrected by dividing the CRAE and CRVE by the MAP to produce the corrected CRAE (cCRAE) and corrected CRVE (cCRVE) respectively.[19] Descriptive statistics in the form of means and standard deviations was performed. Univariate analysis comparing women with pre-eclampsia and the control group at delivery then 1 year were performed making use of independent sample t-tests. A p-value of < 0.05 was considered statistically significant. Ethical approval for the study was obtained from the University of Pretoria Research Ethics Committee (No. 125/2013).

Results

There were 6 536 deliveries at Steve Biko Academic Hospital during the recruitment phase of the study (1 April 2013 – 30 March 2015). Four hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and 106 women were recruited to the larger study (described in methods). Seven women were lost to follow-up and five declined testing at different stages of the study. Data was therefore available for 94 patients. Seventy-three (77.7%) women for whom data was available fulfilled the World Health Organisation (WHO) criteria for the classification of a maternal near miss.[20] Research funding was available for grading of 160 digital photographs. Forty pairs of the best quality digital fundus photographs, at delivery and 1-year post-partum, were selected from the pre-eclamptic and control study groups for grading at the Singapore Eye Research Institute. Fifty-five percent (n= 22) of women in the pre-eclamptic group were diagnosed with chronic hypertension at 1-year. There was a statistically significant difference in the mean arterial blood pressure between the pre-eclamptic and control groups at delivery and 1-year (p < 0.001). The demographic data of the study population is described in Table 1.

Table 1. Demographic data of the study population

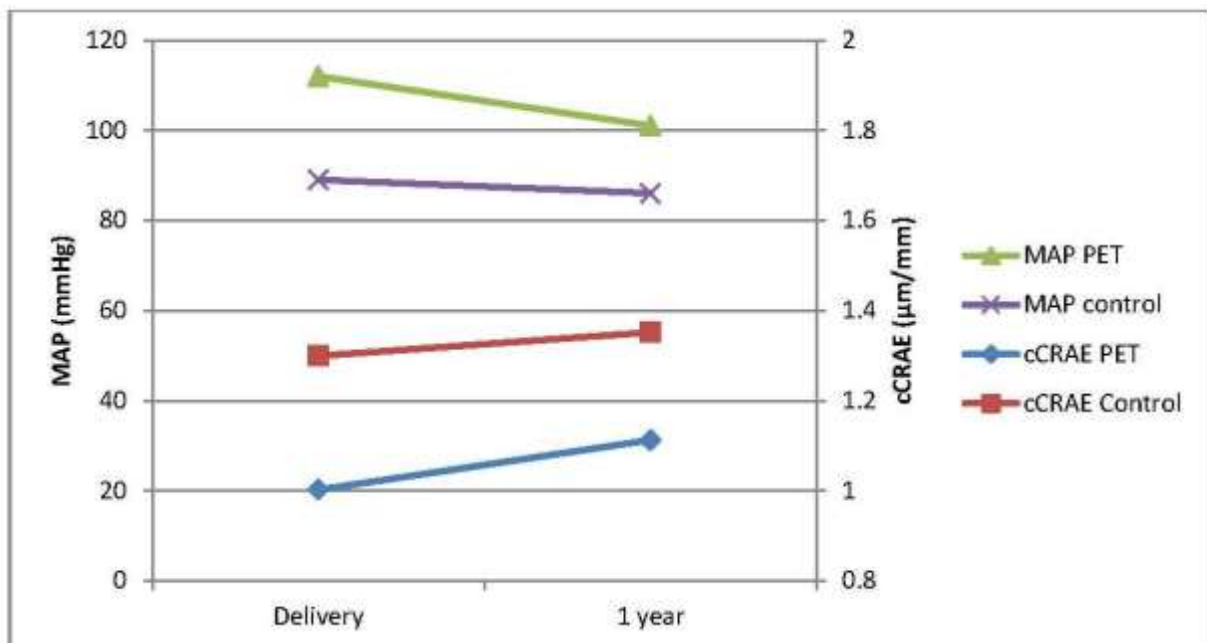|	Pre-eclamptic group (n=40)	Control group (N=40)
Age, years		
Mean (SD)	29.3 (6.4)	29.1 (7.5)
Range	17-41	18-46
Race		
African, n (%)	35 (87.5)	35 (87.5)
Caucasian, n (%)	2 (5.0)	3 (7.5)
Coloured, n (%)	2 (5.0)	2 (5.0)
Indian, n (%)	1 (2.5)	0
Timing of delivery		
< 34 weeks, n (%)	25 (62.5)	0
>34 weeks, n (%)	15 (37.5)	40 (100.0)
Mean birth weight		
Grams, (SD)	1893 (842.1)	3192 (342.8)
Medical Conditions		
Diabetic at 1 year, n (%)	2 (5.0)	0
Hypertensive at 1 year, n (%)	22 (55.0)	1 (2.5)
MAP(mmHg) at delivery mean (SD)	111.73 (7.52)	88.78 (7.44)
MAP(mmHg) at 1-year mean (SD)	100.50 (15.22)	89.92 (7.88)

The mean cCRAE and cCRVE was significantly lower in the pre-eclamptic group compared with the control group both at delivery and 1 year. (Table 2) There was a 0.30µm and 0.24µm difference in cCRAE between the pre-eclamptic and control groups at delivery and 1-year respectively. The difference in cCRVE between the 2 groups at delivery was 0.36µm

and 0.31μm at 1-year. There was a non-significant increase of 0.11μm (p=0.10) in the cCRAE between delivery and 1-year in the pre-eclamptic group. This correlated with a decrease in the MAP between the 2 time-periods. (Figure2a+b) The increase of 0.19μm in the cCRVE in the pre-eclamptic group between delivery and 1-year was statistically significant (p=0.02).

Table 2. Comparison between the retinal artery and vein calibre between the pre-eclamptic and control groups at delivery and 1-year.

	Pre-eclamptic group (n=40)	Control group (n=40)	p-value
Delivery			
MAP (mmHG) Mean (SD)	111.73 (7.52)	88.76 (7.44)	P < 0.001
cCRAE(μm) mean (SD)	1.00 (0.15)	1.30 (0.21)	P < 0.001
cCRVE(μm) mean (SD)	1.46 (0.15)	1.82 (0.38)	P < 0.001
1-year Post-partum			
MAP (mmHG) Mean (SD)	100,50 (15.22)	85.92 (7.89)	P < 0.001
cCRAE(μm) mean (SD)	1.11 (0.22)	1.35 (0.26)	P < 0.001
cCRVE(μm) mean (SD)	1.65 (0.36)	1.96 (0.30)	P < 0.001

Figure 2a Comparison of cCRAE between the pre-eclamptic group and control group showing the relation with MAP

Figure 2b Comparison of cCRVE between the pre-eclamptic group and control group showing the relation with MAP
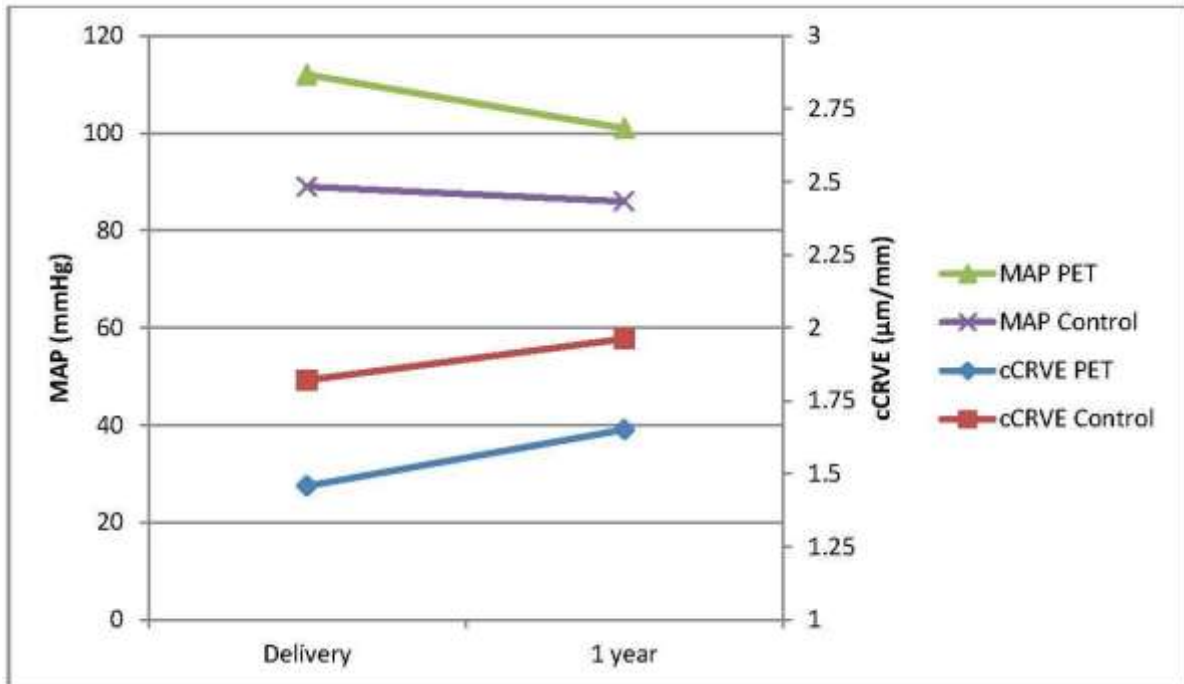
Table 3. Comparison of cCRAE and cCRVE at 1-year between the women with pre-eclampsia and the different clinical sub-groups of women with pre-eclampsia

	cCRAE (μm) at 1 year, mean (SD)	p-value	cCRVE	p-value
Pre-eclamptic group n=40	1.11 (0.22)		1.65 (0.36)	
Early onset pre-eclampsia < 34 weeks n = 24	1.08 (0.23)	0.52	1.57 (0.39)	0.38
Pre-eclamptic women with diastolic dysfunction at 1 year n = 5	1.14 (0.29)	0.77	1.64 (0.41)	0.94
Pre-eclamptic women with WMLs at 1-year n = 17	1.15 (0.24)	0.59	1.74 (0.32)	0.41
Pre-eclamptic women with hypertension at 1-year n = 22	1.04 (0.17)	0.19	1.48 (0.29)	0.06

Sixty percent of women in the pre-eclamptic group developed early onset pre-eclampsia requiring delivery before 34 weeks. A sub-analysis of this pre-eclamptic group showed that these women had an increased risk of developing diastolic dysfunction 1–year after delivery. Table 3 compares the cCRAE and cCRVE of the pre-eclamptic group at 1-year to various clinical sub-groups within the group of women with pre-eclampsia. Although the cCRAE and cCRVE at 1-year were smaller in women with early onset pre-eclampsia requiring delivery < 34 weeks and for pre-eclamptic women with chronic hypertension at 1-year, these differences were not significant. These non-significant findings are possibly due to the small study numbers within the sub-group of pre-eclamptic women.

Discussion

Narrower retinal microvessel caliber seen in women with pre-eclampsia during pregnancy compared to a normotensive control group was first described by Lupton et al.[7,10] Ours is the first study to demonstrate that such retinal arteriolar and venular narrowing in women with pre-eclampsia during pregnancy persists for up to 1-year post-partum. Our study demonstrates longer-term effects of pre-eclampsia on the microvasculature and may provide insights into the higher risks of cardiovascular disease in women with a history of pre-eclampsia.

Vascular endothelial dysfunction is recognised as the key disturbance in the pre-eclamptic disease process. Anti-angiogenic factors such as tyrosine kinase receptor-1 (sFlt-1) are released by the placentas of women with pre-eclampsia. sFLT-1 is secreted into the maternal circulation and has an antagonistic effect on vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). VEGF and PLGF play important roles in maintaining the vascular endothelium and decreased VEGF levels further decrease nitric oxide synthesis resulting in a negative vasodilatory effect. VEGF is also responsible for inducing and maintaining the integrity of fenestrated endothelium in various tissues including the renal glomerulus, and VEGF blockade by sFLT-1 may be a cause for renal damage and a decrease in renal function.[21] Although many of the clinical manifestations of pre-eclampsia resolve after delivery, endothelial dysfunction may persist postpartum.[22] Chambers et al demonstrated that flow mediated dilatation is reduced in women with previous pre-eclampsia compared with uncomplicated pregnancies at a median interval of 3 years postpartum.[23] Endothelial dysfunction has been reported in other studies up to 27 months postpartum.[24,25,26] The mechanisms associated with the failure of blood vessels to maximally dilate include, endothelial dysfunction, a decrease in nitric oxide release, increased responsiveness to the pressor effect of angiotensin II and vasospasm.[23,27,28,29,30] There was a small increase in the cCRAE and cCRVE between delivery and 1-year in the pre-eclamptic group, however this increase was not significant. The sub-group of women who developed early onset pre-eclampsia requiring delivery before 34 weeks and those who

developed chronic hypertension had a smaller cCRAE at 1-year than the combined group of women with pre-eclampsia.

Retinal vascular changes are markers of early pathogenic processes in hypertension and are related to both subclinical and clinical end-organ damage. The association between arteriolar narrowing and development of later hypertension has been described by Ding et al.[31] As a precursor of hypertension, increased peripheral resistance (similar to conditions like pre-eclampsia) occurs primarily in small arteries and arterioles. Therefore, arteriolar narrowing may contribute to an elevation in blood pressure, eventually leading to hypertension and a 'vicious cycle' may develop in which the microcirculation maintains or even amplifies an initial increase in blood pressure.[31,32] This pattern is also evident in women who develop pre-eclampsia where arteriolar narrowing precedes the clinical onset of hypertension during pregnancy.[7] Retinal vessel caliber, during and after pregnancy, remains smaller in pre-eclamptic women than women who are normotensive during pregnancy and a proportion of women with pre-eclampsia during pregnancy will develop chronic hypertension. Fifty-five percent of women in our study remained hypertensive at 1-year. Previous studies have reported that arteriolar constriction and narrowing play a critical role in the earliest stages of hypertension development and retinal vessel wall signs have been associated with systemic markers of inflammation, confirming that inflammation plays a role in the development of hypertension.[33,34] In the Atherosclerosis Risk in Communities (ARIC) Study, normotensive persons aged 49 to 73 years with generalised or focal arteriolar narrowing were 60% more likely to develop hypertension within 3 years than persons without these signs, independent of vascular risk factors.[35] In a population-based cohort study, Smith et al found that generalised retinal arteriolar narrowing was significantly associated with 5-year incident severe (grade 2 or 3) hypertension, independent of other known risk factors for hypertension and baseline blood pressure status.[11] This association was stronger for younger (less than 65 years of age) participants.

The strong, consistent association between pre-eclampsia and future cardiovascular disease was shown in a meta-analysis by Bellamy and colleagues.[13] Coronary and retinal vessels undergo similar changes (such as sclerosis) in patients with hypertension.[36] Assessment of retinal vessels has been shown to correlate with coronary microvascular damage.[36,37] It has been hypothesised that microvascular disease may play a greater role in the development of myocardial ischemia and definite coronary heart disease in women than in men.[38,39] Wong et al found that retinal arteriolar narrowing is related to the risk of coronary heart disease in women but not in men.[40] In this study, every 1-SD decrease in the arteriole-to-venule ratio was associated with a 37% increase in coronary heart disease risk. Similarly, an individual-participant meta-analysis of 22 159 participants from 6 population-based studies has shown that microvascular dysfunction is a greater contributor and predictor of coronary heart disease in women than in men.[36]

In a meta-analysis of 198 252 women with pregnancies affected by pre-eclampsia, the relative risk for the development of stroke after 10 years was 1.81, 95% CI 1.45-2.27.[13] Retinal arteriolar narrowing and decreasing arteriole-to-venule ratio have been shown to predict incident stroke as well as MRI-identified subclinical stroke.[11, 12] The retinal and cerebral microvasculatures have been described as homologus.[41] Similar to changes in retinal vasculature, microvascular changes in the brain may lead to chronic ischemia and the development of white matter lesions. The disruption of the blood-brain barrier of the cerebral microcirculation is believed to be an important pathophysiological feature in the development of cognitive impairment and dementia.[42] Retinal vascular lesions are also believed to reflect a break-down of the blood-retinal barrier. Several studies have reported a relation between retinal vascular abnormalities and cognitive function.[43,44,45] In the hypertensive sub-group of the Cardiovascular Health Study, the presence of any retinopathy (OR 2.10, 95% CI 1.04-4.24) or focal arteriolar narrowing (OR 3.2, 95% CI 1.51-6.02) was associated with an increased risk of dementia.[44]

The detrimental effect of gestational hypertensive disorders on microvasculature is not limited to affected mothers only. Yessil et al have found that children of mothers with gestational hypertensive disorders had narrower retinal arteriolar calibers than children whose mothers were normotensive during their pregnancies.[46] It is believed that adverse fetal exposures linked with gestational hypertension during key vulnerable periods could be responsible in creating a permanent impact on microvascular development.[8] Early microvascular dysfunction is possibly responsible for the adverse hypertensive and cardiovascular profile observed in offspring of mothers who develop pre-eclampsia during pregnancy.

The strength of this study is that this is the first study to show that retinal vessel narrowing associated with pre-eclampsia persists in the post-partum period. The study is limited in that retinal vessel caliber was analysed in only a select group of patients from the larger study evaluating cardiac diastolic function and cerebral white matter lesions after pre-eclampsia, and there were no pre-pregnancy readings of retinal vessel calibre. The smaller numbers means that a possible association between retinal vessel calibre, cerebral white matter lesions and diastolic dysfunction could not be determined accurately.

Conclusion

Retinal arteriolar and venular calibre changes that occur during pregnancies affected by pre-eclampsia persist for up to 1 year post-partum. These changes may be a reflection of permanent, long-term microvascular dysfunction in other organs systems and have been shown to be a predictor of future cardiovascular risk. Pre-eclampsia has a long-term negative effect on maternal health and strategies to prevent the development of pre-eclampsia should be explored further.

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