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

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Abstract

Background: The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, retinal image analysis. The aim of the study was to compare the retinal vessel caliber at delivery and one-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

Methods: Digital photos of the eye were taken at delivery and one-year post-partum. Retinal vessels were analysed and summarised as the corrected central retinal arteriolar equivalent and corrected central retinal venular equivalent.

Results: The corrected central retinal arteriolar equivalent and corrected central retinal venular equivalent were significantly lower in the pre-eclamptic group compared to the control group both at delivery and one-year post-partum ($p < 0.001$).

Conclusion: Retinal artery and venular caliber changes that occur during pregnancies affected by pre-eclampsia persist for up to one-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

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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.^{2–6}

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 (MAP).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 one-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 to 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 to 30 March 2015 and follow-up visits took place from 1 April 2014 to 30 March 2016. Post-partum women (days 2–7 post-delivery) with severe pre-eclampsia were identified every morning during the labour ward round. Women were

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Figure 1. Digitised 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.

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 one-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° non-mydratic retinal fundus camera. Photographs were taken between day 2–7 post-delivery and at one-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. Digital retinal images can be divided into standardised areas around the optic disc for repeatable analysis.¹⁷ The areas around the optic disc are divided into the following zones (Figure 1):

- Zone A – $\frac{1}{2}$ optic disc diameter from the disc margin
- Zone B – Edge of zone A to 1 disc diameter from the optic disc margin
- Zone C – Edge of zone B to 2 disc diameter from optic disc margin

It has been suggested that the smaller retinal vessels which are furthest away from the optic disc are more affected by hypertension.¹⁸ Zone B, which has larger vessels is chosen as the standard area of analysis. 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 six

Table 1. Demographic data of the study population.

	Pre-eclampsic 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 one year, n (%)	2 (5.0)	0
Hypertensive at one 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 one year mean (SD)	100.50 (15.22)	89.92 (7.88)

MAP: mean arterial blood pressure.

largest arterioles and the six largest venules as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively.

The 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 cCRAE and 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 one-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 6536 deliveries at Steve Biko Academic Hospital during the recruitment phase of the study (1 April 2013–30 March 2015). Four hundred and 63 (7.1%) women presented with severe pre-eclampsia and 106 women were recruited to the larger study (described in the Methods section). Seven women were lost to follow-up and 5 declined testing at different stages of the study. Data were therefore available for 94 patients. Seventy-three (77.7%) women for whom data were 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 one-year post-partum, were selected from the pre-eclampsic and control study groups for grading at the Singapore Eye Research Institute. Fifty-five percent (n=22) of women in the pre-eclampsic group were diagnosed with chronic hypertension at one year. There was a statistically significant difference in the MAP between the pre-eclampsic and control groups at

Table 2. Comparison between the retinal artery and vein calibre between the pre-eclamptic and control groups at delivery and one 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)	$p < 0.001$
One 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)	$p < 0.001$

cCRAE: corrected central retinal arteriolar equivalent; cCRVE: corrected central retinal venular equivalent; MAP: mean arterial blood pressure.

delivery and one year ($p < 0.001$). The demographic data of the study population are described in Table 1.

The mean cCRAE and cCRVE was significantly lower in the pre-eclamptic group compared with the control group both at delivery and one year. (Table 2) There was a $0.30\mu\text{m}$ and $0.24\mu\text{m}$ difference in cCRAE between the pre-eclamptic and control groups at delivery and one year respectively. The difference in cCRVE between the 2 groups at delivery was $0.36\mu\text{m}$ and $0.31\mu\text{m}$ at one year. There was a non-significant increase of $0.11\mu\text{m}$ ($p = 0.10$) in the cCRAE between delivery and one year in the pre-eclamptic group. This correlated with a decrease in the MAP between the two time-periods (Figure 2(a) and (b)). The increase of $0.19\mu\text{m}$ in the cCRVE in the pre-eclamptic group between delivery and one year was statistically significant ($p = 0.02$). A sub-analysis of the pre-eclamptic group was performed. The mean cCRAE for pre-eclamptic women at one year with chronic hypertension was $1.043\mu\text{m}$ compared to $1.224\mu\text{m}$ ($p = 0.0084$) for pre-eclamptic women who were normotensive. The mean cCRVE for pre-eclamptic women with chronic hypertension was $1.482\mu\text{m}$ compared to $1.891\mu\text{m}$ ($p = 0.0003$) for those who were normotensive. A receiver operator characteristic curve was used to determine whether cCRAE at delivery

Figure 2. (a) Comparison of cCRAE between the pre-eclamptic group and control group (mean and standard deviation). (b) Comparison of cCRVE between the pre-eclamptic group and control group (mean and standard deviation). cCRAE: corrected central retinal arteriolar equivalent; cCRVE: corrected central retinal venular equivalent.

Table 3. Comparison of cCRAE and cCRVE at one year between the women with pre-eclampsia and the different clinical sub-groups of women with pre-eclampsia.

	cCRAE (μm) at one 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 one year n = 5	1.14 (0.29)	0.77	1.64 (0.41)	0.94
Pre-eclamptic women with WMLs at one year n = 17	1.15 (0.24)	0.59	1.74 (0.32)	0.41
Pre-eclamptic women with hypertension at one year n = 22	1.04 (0.17)	0.19	1.48 (0.29)	0.06

cCRAE: corrected central retinal arteriolar equivalent; cCRVE: corrected central retinal venular equivalent; WMLs: white matter lesions.

would predict hypertension at one year ($\text{MAP} > 110 \text{ mmHg}$). The area under the curve was 0.364 which was not significant. A cCRAE cut-off of $0.974937 \mu\text{m}$ has a sensitivity of 97.9% and a specificity of 34.7%. Therefore cCRAE at delivery is not a good predictor of hypertension at one year.

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 one year after delivery. Table 3 compares the cCRAE and cCRVE of the pre-eclamptic group at one year to various clinical sub-groups within the group of women with pre-eclampsia. Although the cCRAE and cCRVE at one year were smaller in women with early onset pre-eclampsia requiring delivery < 34 weeks and for pre-eclamptic women with chronic hypertension at one 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 one 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.

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.^{21,22} 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 one year. Pre-eclamptic women with chronic hypertension had significantly narrower retinal artery and venular calibers than pre-eclamptic women whose blood pressure normalised after delivery.

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.²³ Assessment of retinal vessels has been shown to correlate with coronary microvascular damage.^{23,24} 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.^{25,26} Wong et al. found that retinal arteriolar narrowing is related to the risk of coronary heart disease in women but not in men.²⁷ In this study, every 1-SD decrease in the arteriole-to-venule ratio was associated with a 37% increase in coronary heart disease risk.

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 homologous.²⁸ Similar to changes in retinal vasculature, microvascular changes in the brain may lead to chronic ischemia and the development of WMLs. 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.²⁹ 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.^{30,31,32} 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.³¹

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 WMLs 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 WMLs 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 one 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.

Declaration of conflicting interests

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Ethical approval

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Guarantor

PSP

Contributorship

PSP, RP, TYW and RCP designed the study and wrote the manuscript. PSP took the fundus photographs and TYW was responsible for grading of fundus photos. JDM carried out the statistical analyses.

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