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Endothelial and kidney function in women with a history of preeclampsia and healthy parous controls: A case control study

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A B S T R A C T

Introduction: Preeclampsia (PE) is a pregnancy related endothelial disease characterized by hypertension and albuminuria. Postpartum endothelial dysfunction often persists in these women. We postulate that in women with a history of PE reduced endothelial dependent vasodilation coincides with attenuated kidney function, as both reflect endothelial dysfunction.

Methods: We assessed endothelial and kidney function in women with a history of PE ($n = 79$) and uncomplicated pregnancies ($n = 49$) at least 4 years postpartum. Women with hypertension, diabetes or kidney disease prior to pregnancy were excluded. Brachial artery flow mediated dilatation (FMD) was measured and analysed by a custom designed edge-detection and wall-tracking software. We measured albumin and creatinine levels in a 24-h urine sample and calculated glomerular filtration rate (GFR) by CKD-EPI.

Results: Women with a history of PE had lower FMD but comparable GFR and albumin creatinine ratio (ACR) compared with controls. Independent of obstetric history, in both controls and women with a history of PE respectively, GFR ($r = 0.19, p = 0.17$ and $r = 0.12, p = 0.29$) and albumin creatinine ratio ($r = 0.07, p = 0.62$ and $r = 0.06, p = 0.57$) did not correlate with FMD.

Conclusion: At least 4 years after pregnancy, women with a history of PE demonstrated decreased flow mediated dilatation when compared to healthy parous controls. In this study, decreased flow mediated dilation however did not coincide with decreased kidney function.

1. Introduction

Preeclampsia (PE) is a pregnancy induced endothelial disease that is characterized by hypertension and albuminuria. Despite the low incidence of 2–8% of pregnancies complicated by PE, it has great impact on maternal and foetal morbidity and mortality (Ghulmiyyah and Sibai, 2012). Worldwide, PE accounts for 14% of maternal deaths, resultantly PE is the second most common cause of maternal death after postpartum haemorrhage (Organization, WH, 2014; Say et al., 2014). In women with a history of PE, endothelial function, as measured by flow mediated dilatation (FMD) is decreased. It improves in the first few weeks postpartum but fails to normalize in the first years after gestation when compared with FMD levels measured in healthy parous controls (Higashi, 2015; Kuscu et al., 2003; John et al., 2001). This indicates only partial reversal of the endothelial dysfunction after a pregnancy complicated by PE. Women with an early onset PE or recurrent PE have more pronounced endothelial dysfunction after pregnancy suggesting

that attenuated endothelial function parallels severity of disease in pregnancy (John et al., 2001). Endothelial dysfunction during a pregnancy complicated by PE also affects kidney function. Kidney dysfunction, reflected by either albuminuria or decreased glomerular filtration rate (GFR), can persist over a period of time after delivery, but most women with a history of preeclampsia maintain good kidney function (Lafayette et al., 1998; Hussein and Lafayette, 2014). Nonetheless, a subgroup of women have persistently decreased kidney function long after their complicated pregnancy (Spaan et al., 2009; Sarah et al., 2010). It may be that, in these women, endothelial dysfunction is reflected in both attenuated kidney function and endothelial dependent flow mediated vasodilation (Deckert et al., 1989). In this study we tested the hypothesis that in women with a history of preeclampsia, kidney function correlates with endothelial dependent flow mediated vasodilation. To this end, we measured endothelial function by brachial flow mediated dilation and kidney function by evaluating 24 h micro albuminuria and GFR, at least 4 years postpartum, in both

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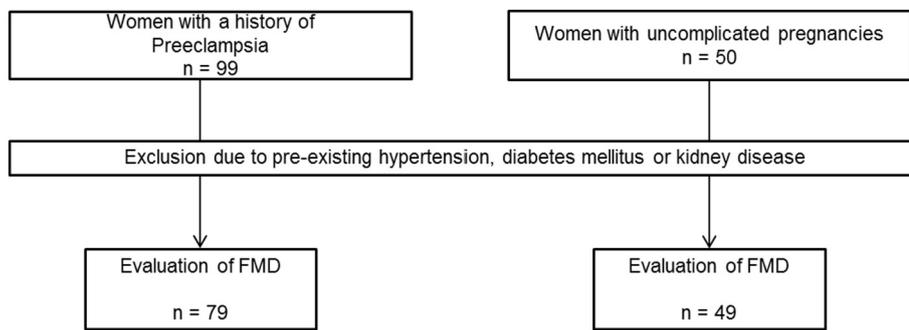


Fig. 1. Flowchart.

women with a history of PE and in a control group of women who had normotensive pregnancies.

2. Methods

In this study, we used a database of women with a history of PE ($n = 99$) who had been tested several years after their pregnancy complicated by preeclampsia. Healthy parous controls ($n = 49$), women with normotensive pregnancies, were recruited through advertisement. All women included were of Northern European Ancestry and completed a follow-up program in 2011. Evaluations were performed in the non-pregnant state at least 4 years after the first (index) gestation postpartum. The study was approved by the Medical Ethics Committee of the Radboud University Medical Centre Nijmegen (CMO 2010/245). All women gave written informed consent. Preeclampsia was defined according to the criteria of the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (*Am. J. Obstet. Gynecol.*, 2000). Neonatal birth weight centile was determined using Dutch reference values for birth weight, corrected for gender and parity (*Nederland Spr*, 2011).

Women were instructed to fast overnight, abstain from alcohol and caffeine for 16 h and not to perform any exercise in the 24 h preceding the measurements. A 24-h urine sample was collected. Upon arrival (body) characteristics were measured and a full medical history was taken. A venous blood sample was taken for measurement of kidney function. Serum creatinine and urine creatinine were measured by an enzymatic colorimetric method (Architect, Abbott Laboratories, Abbott Park, IL, USA) and urine albumin by immunonefelometry (Dade Behring BN II Nefelometer, Siemens, Mississauga, Canada). We estimated GFR by the CKD-EPI equation for female and Caucasian, in which both formulas are dependent on serum creatinine. When serum creatinine was below or equal to 0.7 mg/dl, we used $144 \times (\text{serum creatinine} / 0.7)^{-0.329} \times 0.993^{\text{age}}$. When serum creatinine was above 0.7 mg/dl we used $144 \times (\text{serum creatinine} / 0.7)^{-1.209} \times 0.993^{\text{age}}$. Albuminuria was quantified by the albumin creatinine ratio (ACR) in the 24-h urine sample. Blood pressure was recorded for a period of 30 min at 3-min intervals using a semiautomatic oscillometric device in half-sitting position. Median values of 9 subsequent recordings were used for analysis. Measurements of FMD were taken as previously described by Scholten et al. (2014). All FMD measurements were performed under standardized conditions in a temperature controlled ($\pm 20^\circ\text{C}$), quiet room. Before starting the protocol, subjects rested for at least 15 min, the arm was in an extended position at $\sim 80^\circ$ from the torso and patients were in supine. An automated system ensured a rapid inflation and deflation of the cuff (D.E. Hokanson, Bellevue, WA), with cuff size recommended for the arm circumference and positioned around the forearm, a few centimetres distal to the olecranon. A 10-MHz multifrequency linear array probe attached to a high resolution ultrasound machine (T3000, Terason, Burlington, MA) was used to image the brachial artery in the distal third of the upper arm, 2–5 cm above the antecubital fossa.

The continuous Doppler velocity was simultaneously measured with

the ultrasound at an angle of $< 60^\circ$. First a 1 min baseline recording of brachial artery diameter velocity was measured. Thereafter the forearm cuff was inflated (> 200 mm Hg) for 5 min. The diameter and flow assessments were done 30 s before deflation until 3 min after deflation. FMD analysis was done by custom designed edge-detection and wall-tracking software, independent of investigator bias. Peak diameter was automatically detected according to an algorithm that is described in detail elsewhere (Black et al., 2008). Reproducibility of FMD using this semi-automated software possesses a coefficient of variation of 6.7–10.5%.

2.1. Statistical analysis

All analyses were performed using SPSS version 21.0, property of IBM and supplied by Maastricht University. Data were expressed as group means and standard deviation or medians and interquartile ranges. A p -value < 0.05 was considered to indicate a statistical significant difference. An unpaired t -test was used to analyses differences between groups with normally distributed data. For non-normal distributed data, we used the Mann-Whitney U test. Dichotomic data was analysed with a chi square test. Bivariate correlations were analysed by Spearman's test. A logistic regression was performed to correct for months postpartum, age and the use of antihypertensive drugs.

3. Results

A total of 128 women, 79 with a history of preeclampsia and 49 with an uncomplicated pregnancy were selected after exclusion of women who had hypertension ($n = 18$), diabetes mellitus ($n = 5$) prior to the pregnancy. None had a known history of kidney disease prior to pregnancy (Fig. 1).

Three women with a history of preeclampsia and two healthy parous controls did not collect 24 h urine. We did not estimate microalbuminuria in these subjects. Table 1 shows the characteristics of the

Table 1
Baseline characteristics of women with a history of preeclampsia and uncomplicated pregnancy.

	Uncomplicated pregnancy $n = 49$	History of preeclampsia $n = 79$	p -value
Age (y)	39 \pm 4	35 \pm 4	< 0.001
BMI (kg/m^2)	23 \pm 3	25 \pm 6	0.067
Smoking (%)	5 (10%)	8 (9%)	0.605
Primiparity	5 (10%)	25 (33%)	0.009
Gestational age at delivery (weeks)	39 \pm 2.3	33 \pm 4.5	< 0.001
Birth weight (gram)	3358 [3012–3745]	1786 [1036–2715]	< 0.001
Birth centile	44 [20–65]	24 [5–34]	< 0.001
Months postpartum	96 [70–119]	59 [47–66]	< 0.001
Antihypertensive drugs (%)	0	7 (9%)	0.031

Table 2

Kidney function, endothelial function and blood pressure in women with a history of preeclampsia and uncomplicated pregnancy. Data presented were adjusted for months postpartum, age and use of antihypertensive drugs.

	Uncomplicated pregnancy n = 49	History of preeclampsia n = 79	p-value
GFR (ml/min/1.73m ²)	98 ± 14	105 ± 16	0.55
Albumin creatinine ratio (g/mmol)	0.5 [0.4–1.1]	0.6 [0.3–1.3]	0.92
Flow mediated dilation (%)	9.0 ± 3.6	6.6 ± 3.0	0.001
Baseline diameter a. brachialis (mm)	3.0 ± 0.3	3.0 ± 0.4	0.76
Systolic blood pressure (mm Hg)	110 ± 10	114 ± 11	0.005
Diastolic blood pressure (mm Hg)	71 ± 7	72 ± 8	0.09

study group. Women with a history of PE were on median 4.4 years postpartum, delivered at an earlier gestational age and gave birth to smaller infants at lower birth weight centile compared with healthy parous controls. Controls were on median 8.7 years postpartum and older compared to women with a history of preeclampsia. Women with a history of PE delivered in 53% of cases before 34 weeks gestation and 58% had a child small for gestational age, defined as a growth below the 10th centile. FMD and GFR and micro-albuminuria were similar in women with PE with or without SGA and in women with PE and a delivery before or after 34 weeks pregnancy (see supplemental tables).

Women with a history of preeclampsia had lower FMD (6.6 ± 3.0 vs $9.0 \pm 3.6\%$; $p = 0.001$) and higher systolic blood pressure (114 ± 11 vs 110 ± 10 mm Hg; $p = 0.005$) but similar GFR (105 ± 16 vs 99 ± 14 ; $p = 0.55$) and micro-albuminuria ($0.6 [0.3–1.3]$ vs $0.5 [0.4–1.1]$; $p = 0.92$) when compared with women with an uncomplicated pregnancy (Table 2).

Women with a history of PE also used more antihypertensive drugs (0% vs 8.8% , $p = 0.031$). Baseline diameter values of the brachial artery between groups were comparable ($p = 0.76$). In both women with a history of PE and controls respectively, FMD did not correlate with either albumin creatinine ratio ($r = 0.07$, $p = 0.62$ and $r = 0.07$ $p = 0.51$) or GFR ($r = 0.19$ $p = 0.17$ and $r = 0.15$, $p = 0.19$) (Figs. 2 and 3).

4. Discussion

Women with a history of preeclampsia have decreased FMD, suggesting endothelial dysfunction, but demonstrate similar GFR and urinary albumin loss when compared to healthy parous controls. In contrast to our expectations, we observed no correlation between FMD and

kidney function. Interestingly a correlation has been found between a decreased FMD and proteinuria at 5 years postpartum in women with a history of preeclampsia (Aykas et al., 2015). We were, however, unable to find a correlation between GFR and FMD on the one hand and microalbuminuria and FMD on the other. This could be a result of a different postpartum interval, chosen exclusion criteria or differences in the severity of the gestational disease. A sub-analysis of women with an increased ACR and decreased FMD was not possible due to the small number of women.

Damaged endothelium frequently results in altered permeability of vessels, in the glomerulus, this is clinically apparent as albuminuria (Salmon and Satchell, 2012). The absence of micro albuminuria, a variable that is considered to reflect endothelial disease, particularly if GFR is normal, might suggest that there is endothelial recovery in the kidneys, but that women with a history of preeclampsia could have constitutional reduced FMD or a higher susceptibility for endothelial dysfunction as compared to healthy parous controls. Chronic kidney disease in itself is associated with a decreased endothelial function as measured by FMD (Malyszko, 2010; Verbeke et al., 2007; Verbeke et al., 2011). Even though decreased FMD and microalbuminuria both reflect endothelial dysfunction they may reflect different aspects of endothelial function. Alternatively the endothelial function as assessed by micro-albuminuria may follow a different recovery rate than endothelial function expressed with FMD. The vaso homeostasis of our endothelium is primarily effectuated by nitric oxide which is released in response to increased shear stress caused by changes in blood flow (Boo and Jo, 2003). When the endothelium loses its ability to maintain the delicate balance of circulatory, haemostatic and immunological homeostasis, it becomes vulnerable for the invasion of lipids and leukocytes at locations where lesions occur. A dysfunctioning endothelium, and a decreased availability of nitric oxide, is considered the first step in the development of atherosclerosis and subsequently cardiovascular disease. Although time consuming, FMD is a useful non-invasive reproducible ultrasonographic technique that has been used in many clinical studies and is an indicator of vascular health (Thijssen et al., 2011; Atkinson and Batterham, 2015). During preeclampsia, flow mediated dilatation is decreased, indicating endothelial dysfunction (Guimaraes et al., 2014; Dorup et al., 1999; Vieira et al., 2013; Weissgerber, 2014). During pregnancy, this dysfunction is paralleled by increased permeability leading to extravasation of fluid and oedema formation on the one hand, and the loss of albumin due to glomerular endotheliosis on the other. The endothelium not only seems to be attenuated during the pregnancy affected by preeclampsia, but this seems to persist until several years postpartum (John et al., 2001; Hamad et al., 2007; Paez et al., 2009; Goynumer et al., 2013; Murphy et al., 2014). The relative difference of FMD between women with a history of preeclampsia and controls is generally between 20 and 58%, which is similar in our study (Hamad et al., 2007; Paez et al., 2009; Goynumer

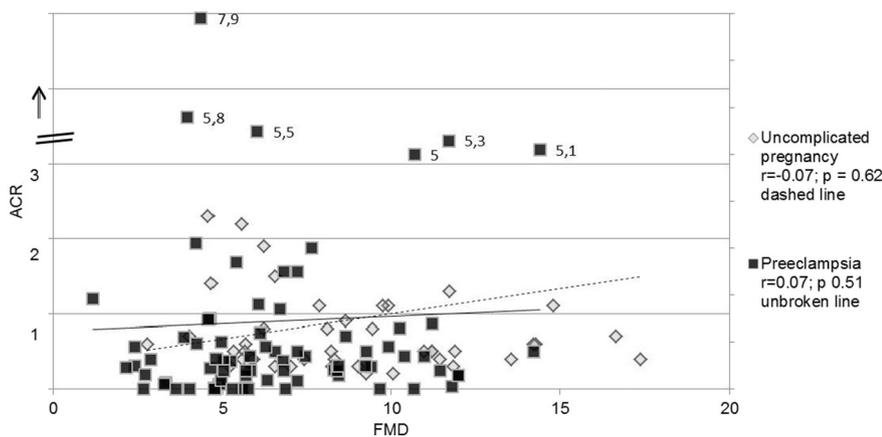


Fig. 2. Correlation between albumin creatinine ratio and flow mediated dilatation (ACR/FMD) in women with a history of preeclampsia and uncomplicated pregnancy. The unbroken trend line represents the women with preeclampsia and the dashed trend line represents controls.

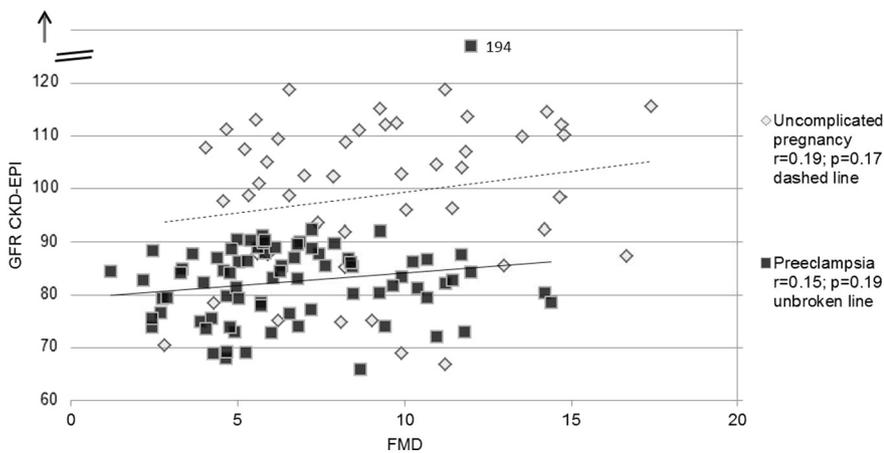


Fig. 3. Correlation between glomerular filtration rate and flow mediated filtration (GFR/FMD) in women with a history of preeclampsia and uncomplicated pregnancy. The unbroken trend line represents de women with preeclampsia and the dashed trend line represents controls.

et al., 2013; Sandvik et al., 2013a).

Endothelial dysfunction is also expressed as decreased kidney function during a pregnancy complicated by preeclampsia and thereafter. Women with preeclampsia exhibit increased albuminuria during pregnancy and have a 4 to 5 times increased risk of end stage kidney disease in later life (Vikse, 2013). Some women maintain decreased kidney function after preeclampsia. This could be either due to undiagnosed pre-existing kidney disease, higher susceptibility or concomitant renal risk factors in these women to develop chronic kidney disease or due to irreversible kidney damage as a consequence of preeclampsia. Most studies on kidney function after preeclampsia have insufficient data on pre-pregnancy GFR or albuminuria values to determine a possible subclinical undetected pre-existing kidney dysfunction (Sarah et al., 2010). Despite the fact that we excluded women with known pre-existing kidney disease, we cannot rule out subtle abnormalities in kidney function. Nonetheless, the observed kidney function does not support the thought that our population studied suffered from kidney dysfunction. Even though some studies show decreased kidney function after pregnancy complicated by preeclampsia (Bar et al., 1999), others do not (Sandvik et al., 2013b; Lampinen et al., 2006). Nonetheless, as a group, women with a history of preeclampsia have an increased risk of end stage kidney disease, even when corrected for common risk factors and confounders such as pre-existing kidney disease, rheumatic disease, hypertension, or diabetes mellitus before pregnancy (Ras et al., 2013). Similarly, flow mediated dilatation appears to be diminished in several, but not all studies in women with a history of PE (John et al., 2001; Sandvik et al., 2013b). It is important to note that all these studies are heterogeneous in nature due to multiple factors namely, measurements at a certain point in time after delivery, differences in severity of preeclampsia and in treatment during pregnancy, but also because of different health policies instituted after pregnancy. It is therefore difficult to draw conclusions based on such heterogeneous studies on the pattern of recovery. Endothelial dysfunction, either expressed by albuminuria or decrease in flow mediated vasodilation, has been investigated in several prospective studies in relation to cardiovascular disease (Ras et al., 2013; Frick et al., 2005; Maruhashi et al., 2013). Meta-analysis detailed that an absolute increase in FMD by 1% decreased the risk of a cardiovascular event in the upcoming 8 years by 13% (Inaba et al., 2010). Moreover, a two-fold increase in albuminuria, another predictor of cardiovascular mortality, is associated with 29% more risk for cardiovascular mortality (Hillege, 2002). Therefore it seems prudent to evaluate flow mediated dilatation and micro-albuminuria in the follow-up of women with a history of preeclampsia as both are considered markers indicating the risk of future cardiovascular disease.

There are some shortcomings of this study that need to be addressed. First, on the one hand, our population contains predominantly women with either early onset disease or concomitant small for

gestational age infancy, both indicators considered to represent more severe disease. This may limit generalizability of our results to all women with a history of preeclampsia. On the other hand, the results might be an underestimation of the prevalence of chronic kidney disease as we excluded women with pre-existing diabetes mellitus, hypertension and kidney disease. Second, the cross-sectional nature of this study may have affected observations. It may be that pace in recovery from pregnancy may be different in the kidney as compared to the endothelium in general, reflected by FMD, which could only be detected by repeated measures over time. Lastly, the age difference between groups can have an effect endothelial function. Endothelial function and its regenerative capacity decrease over time and age related adaptation can gradually be seen in women from the 4th decade of life onwards, and after menopause these changes are even more pronounced (Greenwald, 2007; Harvey et al., 2016; Higashi et al., 2012; Lakatta, 2003; Celermajer et al., 1994; Juonala et al., 2008; Jensen-Urstad and JJ, 2001; Black et al., 2009; Skaug et al., 2013). Both oxidative stress and inflammation, present in arterial aging, seem to cause alterations in the nitric oxide signalling pathway and/or a decreased nitric oxide bioavailability, and cause an age-related decrease in endothelium dependent dilation (Celermajer et al., 1994; Parker et al., 2006; Dick et al., 2009; Donato et al., 2015; Seals et al., 2011). This could have resulted in a smaller difference in endothelial function between groups, for which we opted to correct.

5. Conclusion

Several years after gestation, women with a history of PE have decreased endothelial function as measured by flow mediated dilatation. The decreased FMD does neither relate to decreased glomerular filtration rate nor to micro albuminuria.

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Contribution to authorship

Marc Spaanderman, Julia Spaan and Tom Cornelis were involved in all steps from drafting the work until critically revising the manuscript based on intellectual content. Wieteke Heidema and Ralph Scholten were involved in the intellectual work of designing the study, collecting data and reviewing the manuscript. Veronica Lopes van Balen was in charge of the search question, analysis and writing of the manuscript to the form now presented.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Medical Ethics Committee of the Radboud University Medical Centre Nijmegen (CMO 2010/245). Date of approval 28-08-2010.

Informed consent: For this type of study formal consent was signed by participants.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mvr.2017.11.001>.

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