Renal and vascular function in women with previous preeclampsia: A comparison of low- and high-degree proteinuria

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The degree of proteinuria during preeclampsia has been considered to be a marker of severity of the disease and of endothelial dysfunction. The aim of the study was to assess whether the degree of proteinuria in preeclamptic pregnancy is related to impairment of vascular dilatation and/or kidney function years after the index pregnancy. Thirty women with a history of severe preeclampsia divided into low ($n = 8$, dU-prot < 5 g/day) and high ($n = 22$, dU-prot $\geqslant 5$ g/day) proteinuric groups and 21 women with previous normotensive pregnancy were studied 5–6 years after index pregnancy. Renal function and blood pressure were assessed together with venous occlusion plethysmography, where changes in brachial artery blood flow, induced by intra-arterial infusions of an endothelium-independent (sodium nitroprusside) and an endothelium-dependent (acetylcholine) vasodilator, were measured. The results showed similar renal function in all groups. There was no difference in vasodilation between preeclamptic groups and controls or correlation between degree of proteinuria during index pregnancy and present vasodilation. We conclude that the degree of proteinuria during preeclampsia does not predict vascular dilatation or renal function 5–6 years after preeclamptic pregnancy.

Kidney International (2006) **70,** 1818–1822. doi:10.1038/sj.ki.5001902; published online 27 September 2006

KEYWORDS: preeclampsia; proteinuria; vascular dilatation

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Received 13 February 2006; revised 6 August 2006; accepted 29 August 2006; published online 27 September 2006

Preeclampsia is characterized by high vascular resistance, diminished vascular volume, decreased arterial compliance, and endothelial dysfunction.[1–3] Preeclamptic proteinuria is particularly connected to endothelial dysfunction and the degree of proteinuria is regarded as a marker of the severity of the disease.[4–8] In most cases, elevated blood pressure and proteinuria disappear within a few weeks postpartum;[7] patients with persisting proteinuria are more likely to have underlying renal disease.[9] However, microalbuminuria with otherwise normal renal function has been found in women several years after preeclamptic pregnancy suggesting persisting endothelial injury.[10,11] Recent studies showing impaired vascular dilatation in women several years after preeclamptic pregnancy support this hypothesis.[12–15] In the kidney, the preeclamptic insult results in decrease in renal blood flow and glomerular filtration rate[4,16] and proteinuria, which is considered to reflect the extent and severity of glomerular damage.[17] According to the results of recent studies, structural and charge- and size-selectivity changes in the glomerular filtration barrier appear to account, at least in part, for the development of proteinuria.[4,18,19] A history of preeclampsia has been associated with an increased risk of coronary artery disease (CAD) in women.[20–24] According to Irgens *et al.*,[25] women with preeclampsia who deliver preterm are at an even greater risk of CAD; these women are most often also those who have more considerable proteinuria[26] compared with those delivering at term. Furthermore, we know from studies on non-obstetric patients that nephrotic syndrome is associated with a several-fold increased risk of CAD,[27] and endothelial dysfunction.[28]

In the light of above, the aim of the present study was to investigate, if the degree of proteinuria during preeclamptic pregnancy has an influence on kidney function and vascular dilatation 5–6 years after the index pregnancy.

RESULTS

During pregnancy there was no difference in age or body mass index between the low and high proteinuric groups or the controls (Table 1). This was also true at the time of the follow-up (Table 2). Hypertension and proteinuria appeared

Table 1 | Demographic data during pregnancy

	Patients (dU-prot <5 g) (*n*=8)	Patients (dU-prot >5 g) (*n*=22)	Controls (*n*=21)	Overall ANOVA *P*
Pregnancy				
Age (years)	31±7	33±5	30±4	0.09
Body mass index (kg/m^2, <10 gw)	25±3	24±4	24±2	0.4
Maximum proteinuria in pregnancy (g/day)	1.49 (1.1–3.1)	12.03 (6.0–16.5)	NA	
Systolic BP maximum (mmHg)	177±14*	174±19*	121±10	<0.001
Diastolic BP maximum (mmHg)	109±8*	110±8*	72±7	<0.001
Constant proteinuria, dU-prot>0.3 g (gw)	33±4	31±4	NA	0.1
Blood pressure constantly >140/90 (gw)	33±3	31±4	NA	0.1
S-Urate (μmol/L)	421±65	395±84	NA	0.5
Delivery				
Gestational weeks at delivery	34 (33–38)*	32 (29–36)*	40(40–41)	<0.001
Birthweight (g)	1973 (1545–2613)*	1567 (975–2318)*	3615 (3277–3760)	<0.001

ANOVA, analysis of variance; BP, blood pressure; gw, gestational weeks; NA, non-applicable.
Values are expressed as mean±s.d. or median and interquartile (percentiles 25–75) range. Values of $P<0.05$ are considered significant.
*$P<0.001$ versus controls.

Table 2 | Demographic and kidney function data 5–6 years after preeclampsia

	Patients (dU-prot < 5 g) (*n*=8)	Patients (dU-prot ⩾5 g) (*n*=22)	Controls (*n*=21)	Overall ANOVA *P*
Age (years)	37±7	38±5	36±4	0.4
Body mass index (kg/m^2)	27±5	25±3	24±4	0.3
Blood pressure systolic (mmHg)	124 (115–139)	123 (113–136)*	112 (102–123)	0.03
Blood pressure diastolic (mmHg)	84±8	82±13	75±7	0.04
Mean arterial pressure (mmHg)	95 (92–108)	93 (86–103)*	89 (81–95)	0.048
Smoking >1/day (%)	1/8 (13%)	4/22 (18%)	7/21 (30%)	0.4
Urine volume/24 h (ml)	1675 (1075–2350)	1625 (1100–2275)	1750 (1000–2400)	0.9
dU-alb-Mi (mg/day)	5.5 (4–10)	7 (6–13)	6 (4.5–9)	0.3
U-alb (mg/L)	3.5 (3.4–5)	7.4 (3–6.3)	4 (3–5)	0.8
S-Urate (μmol/l)	283±57	245±64	240±49	0.2
U-Crea (mmol/l)	7.0±2.4	7.6±3.5	7.5±3.4	0.9
Crea-cl (ml/s/1.73 m^2)	1.8 (1.3–2.1)	2.1 (2.0–2.2)	2.1 (2.0–2.5)	0.08
fB-gluc (mmol/l)	4.3 (3.9–4.7)	4.4 (4.2–4.8)	4.4 (4.2–4.6)	0.7

ANOVA, analysis of variance.
Data are presented as mean±s.d. or median and interquartile (percentiles 25–75) range. Values of $P<0.05$ are considered significant.
*$P<0.05$ versus control group.

earlier in the high proteinuric group than in the low proteinuric group, they delivered earlier and had infants with lower birth weight, but statistically this difference was insignificant. Systolic and mean arterial pressure in the high proteinuric group differed significantly compared with the controls ($P=0.03$ and 0.048, respectively). There was no difference in kidney function between the three groups (Table 2). Microalbuminuria (>30 mg/24 h) was found in two women in high proteinuric group, but the difference was not significant ($P=0.64$). The increase in vasodilation was dose-dependent and similar in each group. Increase in vasodilation (%) in response to sodium nitroprusside (SNP) 3 μg/min was 340 (267–368) in the group <5 g, 270 (190–336) in the group ⩾5 g, and 397 (325–451) in the controls ($P=0.009$), to SNP 10 μg/min 522 (494–540) in the group <5 g, 338 (276–729) in the group ⩾5 g, and 581 (386–687) in the controls ($P=0.148$). Endothelium-dependent response to acetylcholine (ACh) 7.5 μg/min was 447 (189–672) in the group <5 g, 313 (219–377) in the group ⩾5 g, and 443 (340–575) in the controls ($P=0.09$) and to ACh 15 μg/min 462 (261–851) in the group <5 g, 365 (233–508) in the group ⩾5 g, and 547 (424–678) in the controls ($P=0.6$); there were no significant differences between the three groups in *post hoc* test. Additionally, there was no correlation between the degree of proteinuria during preeclampsia and the present endothelium-independent or endothelium-dependent vasodilation (Figure 1a and b, respectively). In the group of recurrent preeclampsia ($N=3$), the vasodilation was impaired by 10–26% in endothelium-independent vasodilation ($P=$NS) and in endothelium-dependent vasodilation by 24–26% ($P=$NS) compared to women with a single preeclampsia episode (data not shown).

DISCUSSION

The present study demonstrates that women even with substantial proteinuria during preeclampsia 5–6 years previously have similar vascular function as women with a low

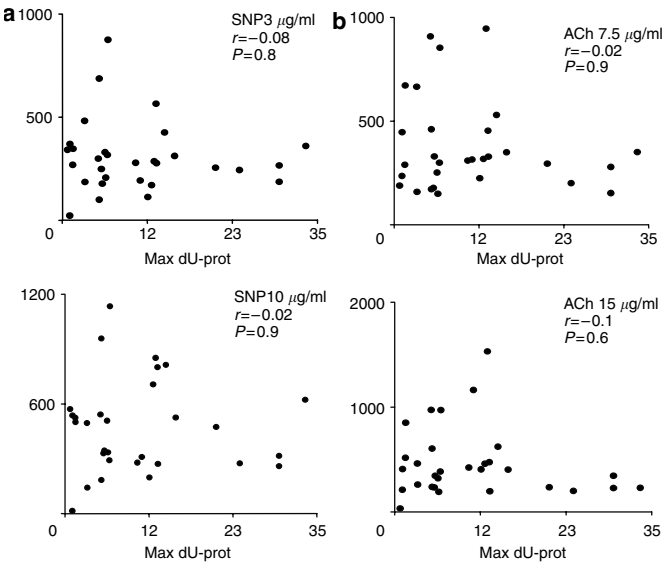

Figure 1 | Correlation between proteinuria and forearm blood flow. (**a**) Correlation between proteinuria during index pregnancy and increase in forearm blood flow in percentage (%) in response to endothelium-independent vasodilator SNP. Values of $P<0.05$ are considered significant. (**b**) Correlation between proteinuria during index pregnancy and increase in forearm blood flow in percentage (%) in response to endothelium-dependent vasodilator ACh. Values of $P<0.05$ are considered significant.

degree of proteinuria and controls measured with venous occlusion plethysmography and intra-arterial vasodilators. We found no impairment in renal function between the groups.

The association between the degree of proteinuria during preeclampsia and postpartum endothelium-dependent and -independent vasodilation has not to our knowledge been studied previously and vascular studies during preeclampsia have not included correlations to the degree of proteinuria.

Preeclampsia is considered severe if proteinuria exceeds 5 g/day[8] and it has been shown that a high degree of proteinuria is associated with earlier onset of the disease and delivery and a higher rate of prematurity problems.[26] Proteinuria was pregnancy-related, as even proteinuria up to 33 g (per 24 h) disappeared postpartum and renal function totally recovered. Renal function test results were normal in the studied women, which is consistent with the results of previous studies where the degree of preeclamptic proteinuria has been low to moderate[29,10,11] and even massive.[7]

Microalbuminuria is considered to be a marker of generalized vascular dysfunction[30] and is an independent risk factor of cardiovascular disease.[31–33] Two follow-up studies have shown an increased incidence of microalbuminuria (14–42%) in women with previous preeclampsia years after the index pregnancy.[10,11] In our study, there was no difference between the groups in the incidence of microalbuminuria 5–6 years after the index pregnancy. The difference between these study results could be explained by the higher incidence of chronic hypertension; 20% in the study by Nisell *et al.*[10] in their preeclampsia group compared with our 2/30 (7%).

Five to six years after preeclamptic pregnancy, there were no significant differences in vasodilatory capacity between the low and high proteinuric groups. Hence, even if the degree of glomerular impairment as defined by proteinuria during preeclampsia was extensive in several of the women, it does not seem to predict poorer endothelial vasodilatory function in later life; the endothelium appears to recover equally after high or low proteinuric disease. Another feature closely related to endothelial function is blood pressure. In this regard, our preeclamptic study groups did not differ significantly from each other during preeclampsia. After 5–6 years, blood pressure was higher in the high proteinuric group than in the controls. Hence, we cannot rule out the possibility that women in the high proteinuric group may develop endothelial dysfunction more easily later in life in parallel with increase in blood pressure, as previous studies have shown preterm-delivering preeclamptic women to be at an especially high risk for later CAD.[20–23] Interestingly, women with recurrent preeclampsia have been shown to have even more limited vasodilatory capacity (12). As a sign of a more compromised status in the vasculature, it may also illustrate a higher risk for later CAD. Our study showed decrease in both endothelium-independent and endothelium-dependent vasodilation in the group of recurrent preeclampsia, although the number of patients was too small to draw any conclusions. In addition, to accurately study a group of patients with recurrent preeclampsia, the study cannot include women in fertile age as the future pregnancy number and outcome is not known. Limitations of our study are the relatively small numbers of patients and controls and the fact that we were not able to study their vascular function during pregnancy. On the other hand, in this study we have used an accurate and invasive method to study vascular dilatation and it involves one of the largest study populations (relatively young women) in whom this laborious method has been used.

In conclusion, the degree of preeclamptic proteinuria does not seem to have a predictive value to vasodilatory capacity or renal function 5–6 years after preeclamptic pregnancy.

MATERIALS AND METHODS

Pregnancy data was collected from the hospital records of women treated for preeclampsia (IC-10 diagnosis O14.1) at Helsinki University Central Hospital during the period 1996–1998. Only women with a well-documented 24-h urinary output of protein (dU-prot) were included. Subjects with concomitant disease such as chronic hypertension, kidney disease, coagulation disorders, diabetes, or a history of gestational diabetes were excluded. Of the 83 eligible subjects, 21 refused to participate and 32 were not reached. The study group thus consisted of 30 women, divided into two groups according to maximal total diurnal proteinuria, that is, 'low' <5 g/day (median dU-prot 1.5 g, range 0.75–4.97 g/day) and 'high' $\geqslant 5$ g/day (median dU-prot 12.0 g, range 5.1–33.44 g/day) proteinuria groups. The control group ($n=21$) consisted of subjects selected at random from women with a record of normal,

uncomplicated pregnancy during the same time period. All women were examined 5–6 years after the index pregnancy. Two women with hypertension, diagnosed after preeclamptic pregnancy, withheld their antihypertensive medication for three days before the study. None of the women were on estrogen substitution. Non-steroidal anti-inflammatory drugs and other drugs affecting endothelial function were withheld for 7 days before the study. The Ethics Committee of Helsinki University Central Hospital approved the experimental protocol and every woman gave her written consent of participation to the study.

Endothelial function was assessed *in vivo* by measurement of forearm arterial blood flow by venous occlusion plethysmography during intra-arterial vasodilator infusion.[34–36] Measurements were performed in a quiet, temperature-controlled (20–21°C) room in the morning after an overnight fast (minimum 12 h). The endothelium-independent vasodilator SNP and the endothelium-dependent vasodilator ACh were infused into the brachial artery in the following sequence: SNP at 3 and 10 μg/min for 6 min each, ACh at 7.5 and 15 μg/min in the same way. Saline was infused before and between the two vasodilators to allow the flow to return to the basal level before the next infusion. Forearm blood flow was measured during the last 3 min of every 6-min infusion period and the mean of the last five recordings was used in the analysis. Blood pressure was measured after a 30-min rest in a supine position with a calibrated oscillometric manometer (OMRON M4, HEM-722C1-E) by a trained midwife. One of three cuff sizes (small, medium, large) was used according to the manufacturer's guidelines. Blood samples for assay of uric acid and blood glucose were taken and 24-h urine sampling was started. The collected urine was analyzed next day with simultaneous analysis of 24 h albumin excretion (immunoturbidimetric 'in-house' analysis [SFS-EN ISO/IEC 17025]), and both urine and serum creatinine (enzymatic colorimetric, accredited method [SFS-EN ISO/IEC 17025]).

Statistics

Normally distributed data is given as mean $\pm$ s.d., whereas non-normally distributed data is given as median with interquartile range (25th and 75th percentiles). Student's *t*-test was used for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data in the two groups when no pregnancy data on the controls was available. For comparisons between the controls and the two patient groups, one-way analysis of variance was performed, followed by the Bonferroni *post hoc* test for normally distributed data. Kruskal–Wallis analysis of variance by ranks was used for non-normally distributed data. Frequencies of categorical data in the three groups were compared by means of Fisher's exact test. The correlation between proteinuria during index pregnancy and flow change (%) in response to vasodilators was calculated with Spearman rank correlation coefficient (r_s). Calculations were performed with NCSS 2000 software (Number Cruncher Statistical Systems, Kaysville, UT, USA). The power to detect a 1.5-fold difference in vasodilation at a *P* level of 0.05 was 80%. A *P*-value <0.05 was considered statistically significant.

ACKNOWLEDGMENTS

We thank Eija Kortelainen for her assistance in physical measurements and for laboratory work. This work was supported by a special governmental grant for health sciences research (no. 2220), the Folkhälsan Research Foundation, the Else and Wilhelm Stockmann Foundation and Foundation for Obstetric and Gynecological Research, the Karolinska Institute, Stockholm, Sweden. There is no conflict of interest with any of the authors.

REFERENCES

1. Hibbard JU, Shroff SG, Lang RM. Cardiovascular changes in preeclampsia. *Semin Nephrol* 2004; **24**: 580–587.
2. Elwan-Taşpinar A, Franx A, Bots ML *et al.* Central hemodynamics of hypertensive disorders of pregnancy. *Am J Hypertens* 2004; **17**: 941–946.
3. Lyall F, Greer IA. The vascular endothelium in normal pregnancy and pre-eclampsia. *Rev Reprod* 1996; **1**: 107–116.
4. Moran P, Lindheimer MD, Davison JM. The renal response to preeclampsia. *Semin Nephrol* 2004; **24**: 588–595.
5. Lafayette R. The kidney in preeclampsia. *Kidney Int* 2005; **67**: 1194–1203.
6. Chan P, Brown M, Simpson JM, Davis G. Proteinuria in preeclampsia: how much matters? *Br J Obstet Gynaecol* 2005; **112**: 280–285.
7. Chua S, Redman CWG. Prognosis for pre-eclampsia complicated by 5 g or more of proteinuria in 24 h. *Eur J Obstet Gynecol* 1992; **43**: 9–12.
8. Anonymous. Prognosis Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin no 33. *Obstet Gynecol* 2002; **99**: 159–167.
9. Murakami S, Saitoh M, Kubo T *et al.* Renal disease in women with severe preeclampsia or gestational proteinuria. *Obstet Gynecol* 2000; **96**: 945–949.
10. Nisell H, Lintu H, Lunell NO *et al.* Blood pressure and renal function seven years after pregnancy complicated by hypertension. *Br J Obstet Gynaecol* 1995; **102**: 876–881.
11. Bar J, Kaplan B, Wittenberg C *et al.* Microalbuminuria after pregnancy complicated by pre-eclampsia. *Nephrol Dial Transplant* 1999; **14**: 1129–1132.
12. Chambers JC, Fusi L, Malik IS *et al.* Association of maternal endothelial dysfunction with preeclampsia. *JAMA* 2001; **285**: 1607–1612.
13. Agatisa PK, Ness RB, Roberts JM *et al.* Impairment of endothelial function in women with a history of preeclampsia; an indicator of cardiovascular risk. *Am J Physiol* 2004; **286**: H1389–1393.
14. Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. *Br J Obstet Gynaecol* 2003; **110**: 1029–1031.
15. Lampinen K, Rönnback M, Kaaja R, Groop P-H. Impaired vascular dilatation in women with a history of preeclampsia. *J Hypertens* 2006; **24**: 751–756.
16. Karumanchi SA, Maynard SE, Stillman IE *et al.* Preeclampsia: a renal perspective. *Kidney Int* 2005; **67**: 2101–2113.
17. Keane WF. Proteinuria; Its clinical importance and role in progressive renal disease. *Am J Kidney Dis* 2000; **35**: S97–S105.
18. Lafayette RA, Druzin M, Sibley R *et al.* Nature of glomerular dysfunction in pre-eclampsia. *Kidney Int* 1998; **54**: 1240–1249.
19. Moran P, Baylis PH, Lindheimer MD, Davison JM. Glomerular ultrafiltration in normal and preeclamptic pregnancy. *Am J Soc Nephrol* 2003; **14**: 648–652.
20. Hannaford P, Ferry S, Hirsch S. Cardiovascular sequelae of toxaemia of pregnancy. *Heart* 1997; **77**: 154–158.
21. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001; **357**: 2002–2006.
22. Wilson BJ, Watson MS, Prescott GJ *et al.* Hypertensive diseases in pregnancy and risk of hypertension and stroke in later life: results from cohort study. *Br Med J* 2003; **326**: 845–851.
23. Haukkamaa L, Salminen M, Laivuori H *et al.* Risk for subsequent coronary artery disease after preeclampsia. *Am J Cardiol* 2004; **15**: 805–808.
24. Anonymous. Report of the national high blood pressure education programme working group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000; **183**: s1–s22.
25. Irgens HU, Reiaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: a population based cohort study. *BMJ* 2001; **323**: 1213–1216.
26. Newman MG, Robichaux AG, Stedman CM *et al.* Perinatal outcomes in preeclampsia that is complicated by massive proteinuria. *Am J Obstet Gynecol* 2003; **188**: 264–268.
27. Ordonnez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with a nephrotic syndrome. *Kidney Int* 1992; **44**: 638–642.
28. Stroes ESG, Joles JA, Chang PC *et al.* Impaired endothelial function in patients with nephrotic range proteinuria. *Kidney Int* 1995; **48**: 544–550.
29. Spaanderman MEA, Ekhart THA, van Eyck J *et al.* Latent hemodynamic abnormalities in symptom-free women with a history of preeclampsia. *Am J Obstet Gynecol* 2000; **182**: 101–107.

30. Karalliedde J, Viberti G. Microalbuminuria and cardiovascular risk. *Am J Hypertens* 2004; **17**: 986–993.
31. Gerstein HC, Mann JFE, Yi Q *et al*. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**: 421–426.
32. Romundstad S, Holmen J, Kvenild K *et al*. Microalbuminuria and all-cause mortality in 2089 apparently healthy individuals: a 4.4-year follow-up study. The Nord–Trondelag Health Study (HUNT), Norway. *Am J Kidney Dis* 2003; **42**: 466–473.
33. Garg JP, Bakris GL. Microalbuminuria: marker of vascular dysfunction, isk factor for cardiovascular disease. *Vasc Med* 2002; **7**: 35–43.
34. Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. *Br J Clin Pharmacol* 2001; **52**: 631–646.
35. Benjamin N, Calver A, Collier J *et al*. Measuring forearm blood flow and interpreting the responses to drugs and mediators. *Hypertension* 1995; **25**: 918–923.
36. Walker HA, Jackson G, Ritter JM, Chowienczyk PJ. Assessment of forearm vasodilator responses to acetylcholine and albuterol by strain gauge plethysmography: reproducibility and influence of strain gauge placement. *Br J Clin Pharmacol* 2001; **51**: 225–229.