High-Normal Estimated Glomerular Filtration Rate in Early-Onset Preeclamptic Women 10 Years Postpartum

Nina D. Paauw, Jaap A. Joles, José T. Drost, Marianne C. Verhaar, Arie Franx, Gerjan Navis, Angela H.E.M. Maas, A. Titia Lely

Abstract—Women with a history of preeclampsia have a 5- to 12-fold increased risk to develop end-stage kidney disease. Previous observations in small cohorts suggest that former preeclamptic (fPE) women have subtle abnormalities in renal hemodynamics and renal function, which might predispose them to renal failure in later life. In this study, we analyzed renal function in a cross-sectional cohort consisting of former early-onset preeclamptic (fPE, n=339) and former healthy pregnant women (fHP, n=332), overall with a mean age of 39 years at 10 years postpartum. Estimated glomerular filtration rate (eGFR), assessed by the modification of diet in renal disease (MDRD) and chronic kidney disease–epidemiology (CKD-epi) equations, and urinary protein:creatine ratios were assessed 10 years postpartum. Median MDRD and CKD-epi eGFR did not significantly differ between fHP and fPE groups, whereas a comparison of distribution of eGFR revealed a shift toward a high-normal MDRD eGFR in the fPE group ($\chi^2$, $P=0.02$) with the same trend for CKD-epi eGFR ($\chi^2$, $P=0.18$). The odds ratio for fPE women having MDRD eGFR >110 mL/min per 1.73 m$^2$ was 1.6 (1.1–2.4). In addition, the median urinary protein:creatinine ratio was slightly higher in fPE (8.5 versus 7.1 mg/mmol; $P=0.01$) and correlated positively with both MDRD and CKD-epi eGFR in fPE women. No increased incidence of CKD in fPE women was observed. In conclusion, we demonstrate subtle changes in renal function in former early-onset preeclamptic women 10 years postpartum, characterized by a high-normal eGFR and a slightly higher protein excretion. Whether these subtle differences predispose to or predict long-term renal function loss in fPE women remains to be investigated.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2668.
an increased occurrence of microalbuminuria in fPE =7 years postpartum (31% versus 7%). However, some studies that were not included in the meta-analysis report the incidence of proteinuria in fPE being low and similar to that of fHP women.7,11

The conflicting results of the different studies on renal function and albuminuria after preeclampsia might be because of small-sized studies and heterogeneity within the fPE group, including a case-mix of early and late preeclampsia. We, therefore, aimed to study renal function in a large cohort at 10 years postpartum of well-characterized former early-onset PE women. eGFR and urinary protein loss were assessed in participants of the PREVFEM study (Preeclampsia Risk Evaluation in Females), a cross-sectional cohort consisting of former early-onset PE women (n=339) and fHP women (n=332).

Materials and Methods

Study Population

Our study population consisted of fPE women and fHP controls who participated in the PREVFEM study (The Netherlands National Trial Register http://www.trialregister.nl; trial registration number: 2668). As described, these women were selected from the obstetric database at the Isala Klinieken Zwolle by delivery between 1991 and 2007.12 They were selected based on age at delivery and date of delivery aiming at an average inclusion of 10 years postpartum. A total of 339 of 515 invited fPE women (response rate 64%), and 332 of 810 fHP women inclusions of 10 years postpartum. A total of 339 of 515 invited fPE women (response rate 41%) were eligible and willing to participate.

Study Protocol

All participating women attended a cardiovascular screening program between April 2009 and May 2010. Participants were asked to fill in a questionnaire on their obstetric history, medical history, medication use, and lifestyle. Physical examination was performed by trained nurses at the outpatient clinic of the Department of Cardiology. The examination consisted of measurements of length, weight, waist and hip circumferences, pulse rate, and blood pressure. Blood pressure (Omron M7) was measured with the appropriate cuff in both arms in a sitting position after a period of 10 minutes’ rest. The mean of 3 blood pressure measurements is reported. A resting ECG (Welch Allyn) was taken, and fasting blood and morning urine samples were collected for laboratory testing. Antihypertensive medication was classified as being an angiotensin-converting enzyme inhibitor/angiotensin receptor blockade or another class of blood pressure–lowering medication. All data were collected in an electronic case report form, provided by Diagram BV Zwolle. Findings on blood pressure and ECG were previously assessed and published.12,13

Blood and Urine Analyses

Blood lipid profile, glucose, C-reactive protein, and fibrinogen were locally analyzed, and the results have been reported.12 Creatinine levels in urine and serum were analyzed using a colorimetric enzymatic method (Modular P8000). Urinary protein was measured using a turbidimetric method 9 (Modular P8000). Urinary protein:creatinine ratio (PCR) was calculated by dividing total protein in the urine (mg/L) by the concentration of creatinine in the urine (mmol/L), resulting in ratio mg/mmol. Significant proteinuria was defined as PCR >30 mg/mmol.4 We calculated eGFR using the CKD-Epidemiology Collaboration creatinine equation (eGFR=141×min [Scr/0.7, 1]×0.328×max [Scr/0.7, 1]−1.209×0.993 Age×1.018 with Scr in mg/dL, min indicating the minimum of Scr/k or 1 and max indicates the maximum of Scr/k or 1)15 and modification of diet in renal disease (MDRD) formula (eGFR=186×[Creat/88.4]−1.154×[Age]−0.203×0.742 with Scr in mg/dL).16 The ethnicity of the women was not recorded. On the basis of the general demographic characteristics of the catchment region of the hospital, we assumed that all women were white. A high-normal eGFR was defined as eGFR over 110 mL/min per 1.73 m²; which is 2 SD above the mean eGFR of healthy women as reported in the population-based studies.17,18 CKD was defined as eGFR <60 mL/min per 1.73 m².19

Data Analysis

Parametric data are presented as means±SD and nonparametric data as mean (25th to 75th percentile). Categorical data are expressed as percentages. Normality of distributions was tested by the Shapiro–Wilk test. For parametric and nonparametric data, we used the Student t test or Mann–Whitney U-test, respectively, and for the categorical data, we used the χ² test. The differences in the distribution of eGFR between fPE and fHP were analyzed by the χ² test after ranking to obtain 10 equal groups. In the logistic regression analyses, we corrected for years postpartum and oral contraceptive (OC) use and the combination of the 2. In addition, we corrected for mean arterial pressure and diabetes mellitus as single covariates to investigate the effect of those variables on the eGFR as we expect both variables to be involved in the pathway between preeclampsia and long-term changes in eGFR. All analyses were repeated after the exclusion of participants with documented DM. Pearson correlation was used to assess association between eGFR and other variables. The analyses were performed using the statistical package SPSS 20 (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

The pregnancy characteristics and baseline follow-up characteristics of the fHP and fPE groups are summarized in Table 1.12 The age at delivery was significantly higher in the fPE group, and the index pregnancy was the first pregnancy in a higher percentage of women in the fPE group. The duration of the
pregnancy in the fPE women was significantly lower with significantly lower birth weights (as an expected result of early-onset preeclampsia). At the moment of follow-up, the women in the fHP and fPE groups had comparable ages (mean 39 years), but because of the higher age at delivery, the fPE women had shorter interval between the index pregnancy and the follow-up. At this time point, fPE women had experienced a significantly lower number of pregnancies. The cardiovascular screening showed that blood pressure was significantly higher in the fPE women, and a significantly higher percentage of fPE women used antihypertensive medication. BMI and waist:hip ratio did not differ between groups, and metabolic profiles were comparable. The incidence of other cardiovascular risk factors such as diabetes mellitus and current smoking were similar, whereas the use of OC was significantly lower in the fPE group.

### High-Normal eGFR in fPE

At follow-up, the median eGFR, calculated using both the MDRD and CKD-epidemiology (CKD-epi) formula, did not significantly differ between groups (Table 2). The eGFR distributions were not normally distributed with a skewness...
to right for the MDRD and a skewness to left for the CKD-epi (Figure S1 in the online-only Data Supplement). Overall, comparison of the distribution of MDRD eGFR of the fHP and fPE showed significant differences between the 2 groups ($\chi^2$, $P=0.02$), with a clear shift toward higher eGFR in the fPE group (Figure 1A). Exclusion of participants with DM ($n=6$) did not influence this finding ($\chi^2$, $P=0.04$). A total of 83 fPE women (24.6%) and 56 fHP women (16.9%) had an MDRD eGFR above the 110 mL/min per 1.73 m$^2$. The calculated odds ratio (OR) for fPE women to have an MDRD eGFR $>$110 mL/min per 1.73 m$^2$ is 1.6 (95% confidence interval, 1.1–2.3; $P=0.02$) and remains the same after correction for possible confounders, including the years postpartum, use of OC, mean arterial pressure, and diabetes mellitus (Table 4).

Only one woman in the fPE group had an eGFR meeting CKD criteria. A trend toward a high normal fPE was also observed by comparison of the distributions of CKD-epi eGFR between fHP and fPE ($\chi^2$, $P=0.18$; Figure 1B). The CKD-epi eGFR is above the 110 mL/min per 1.73 m$^2$ in 119 (35.2%) of the fPE women and 95 (28.8%) of the fHP women. The OR for fPE to have a high-normal CKD-epi eGFR compared with fHP was only significantly increased after adjustment for mean arterial pressure, indicating the important role of systemic arterial pressure on glomerular hemodynamics (Table 4).

Angiotensin-converting enzyme inhibitor/angiotensin receptor blockade use did not affect MDRD and CKD-epi eGFR in both the groups (Table 3), and adjustment of the OR for angiotensin-converting enzyme inhibitor/angiotensin receptor blockade did not substantially change our findings (OR [95% confidence interval] for MDRD $>$110 mL/min per 1.73 m$^2$: 1.6 [1.09–2.35], $P=0.02$; OR [95% confidence interval] for CKD-epi $>$110 mL/min per 1.73 m$^2$: 1.36 [0.97–1.89], $P=0.07$). OR for both MDRD and CKD-epi changed slightly after the exclusion of the diabetic participants (Table S1). We found that both eGFR MDRD and CKD-epi eGFR were negatively correlated with systolic and diastolic blood pressure in fHP, whereas this correlation was absent in fPE. BMI was not associated with either MDRD eGFR or CKD-epi eGFR.

**Higher Urinary Protein Excretion in fPE**

The median urinary PCR in fPE was slightly but significantly higher in fPE women compared with fHP (fPE: 8.5 [6.3–13.0] versus fHP: 7.1 [5.5–10.5], $P<0.01$; Figure 2). There was no difference in the incidence of significant proteinuria between groups (fPE: 3.68% versus fHP: 3.70%). We observed a positive correlation between PCR and eGFR in fPE women (MDRD eGFR: $r=0.17$, $P<0.01$; CKD-epi eGFR: $r=0.14$, $P=0.01$), whereas this correlation was absent in fHP women.
Kidney damage on the long-term. Whether the high-normal glomerular capillary pressure, which can induce progressive hyperfiltration, is characterized by increased occurrence of CKD in fPE women. As yet, our observation has no clinical implications because these do not help to identify women at high risk for the development of CKD and ESKD, it will be interesting to rescreen the fPE women after 20 years postpartum.

Although all observed renal function abnormalities in this study are subtle, our finding of high-normal eGFR in fPE women raises the question whether this has a mechanistic contribution to the higher risk of ESKD. Although some previous reports on eGFR after preeclampsia showed a decreased eGFR or no differences in eGFR, our finding of high-normal eGFR in former early-onset preeclampsia only subtle renal function alterations are present without an increased occurrence of CKD in fPE women. As yet, our observation has no clinical implications because these do not help to identify women at high risk for the development of CKD and ESKD, it will be interesting to rescreen the fPE women after 20 years postpartum.

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Discussion

In this study, we demonstrate a shift of eGFR distribution to the high-normal range and slightly higher protein excretion in former early-onset PE women 10 years postpartum. This is the first study on renal function in a large cohort of well-characterized fPE women compared with age-matched controls and shows that at 10 years after early-onset preeclampsia only subtle renal function alterations are present without an increased occurrence of CKD in fPE women. As yet, our observation has no clinical implications because these do not help to identify women at high risk for the development of CKD and ESKD, it will be interesting to rescreen the fPE women after 20 years postpartum.

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disturbance in tubuloglomerular feedback that may play a role in the development of hyperfiltration in fPE women. Factors that might contribute to this process in fPE women include enhanced proximal reabsorption and efferent arteriolar vasoconstriction as a result of increased angiotensin II sensitivity. In addition, metabolic disturbances might play a role in the development of hyperfiltration in fPE women. The combination of raised vasopressin and glucagon was showed to induce hyperfiltration. Although we were not able to measure these hormones in our population, fPE women were previously reported to have unfavorable metabolic profiles. These, however, remain speculations as exact pathophysiologic mechanisms of glomerular hyperfiltration are not fully understood.

In this study, we also observed a slight increase in urinary protein within the normal range in fPE women loss by measuring PCR. Proteinuria after preeclampsia might be caused by underlying kidney disease or by kidney damage induced during the pregnancy. On the other hand, proteinuria can develop over the years as a result of an unfavorable cardiovascular profile characterized by endothelial dysfunction, which is reported after preeclampsia. Whether tubular or glomerular mechanisms lead to proteinuria in fPE women is unclear. Interestingly, a unifying hypothesis on hyperfiltration and proteinuria has been advanced in the context of diabetes mellitus. If a similar pathophysiology would be present in fPE women, an implication could be that renin–angiotensin–adrenocortical system blockade is the preferred mode of antihypertensive treatment, as this reduces not only systemic blood pressure but also glomerular pressure and proteinuria.

Our study has a few limitations. First, the use of GFR estimations is difficult in the setting of relatively healthy populations and generally underestimates normal to high-normal eGFR. The CKD-epi is, in general, better accepted for the general population, but we found that this formula shows a non-Gaussian distribution skewed to the left (negatively skewed). Opposite to this, while using the same parameters for calculation, the MDRD eGFR distributions showed skewness to the right (positively skewed), which allowed us to better distinguish between groups in high-normal ranges and indicates that MDRD could be more suited to detect high-normal eGFR. This might explain that we only found a significant shift of eGFR distribution to the high-normal range for MDRD and not for CKD-epi. However, the CKD-epi eGFR curves suggest the same trend (Table S1) and the OR for fPE to have a CKD-epi eGFR >110 mL/min per 1.73 m² compared with controls became significant after correction for mean arterial pressure. Second, we have no preconception data available to study to what extent these abnormalities observed postpartum are the result of pre-existing abnormalities or because of damage induced by the preeclampsia. In addition, we have no reliable data available on total number of PE pregnancy to study the effect of repetitive PE on eGFR while other studies already showed a dose–response curve on cardiovascular and renal prognosis. Other limitations are the slight differences in pregnancy to follow-up interval between the fHP and fPE groups, the absence of urinary albumin measurement, and the absence of data on social economic status, which is correlated with a lower eGFR. In a subgroup of the PREVFEM cohort, it was suggested that the fPE might have a higher social economic status because they were reported to have a higher education, but in the full cohort, we could not find any differences in modifiable indicators of socioeconomic status affecting the eGFR (BMI and metabolic profile). Finally, we can only speculate about the fact whether high-normal eGFR after fPE leads to long-term renal function decline as we do not yet have longitudinal follow-up. The subtle findings at 10 years postpartum might be explained by the fact that at this time point, the premenopausal status of the women still protects against the development of cardiovascular disease.

The strength of our study is the large number of participants, which exceed the numbers of participants in all previous studies that investigated renal function after preeclampsia. The cohort was well characterized, with reliable pregnancy documentation and intensive follow-up at 10 years. Our population consisted of early-onset preeclamptic women, which are most severely affected by cardiovascular disease in later life and are, therefore, perhaps more prone to develop abnormalities in kidney function on the long term.

Perspectives

Our study shows that early-onset fPE women have subtle renal abnormalities at 10 years postpartum characterized by a high-normal eGFR which is accompanied by a slight increase in urinary protein loss within the normal range without an increased incidence in CKD. Whether these subtle differences might predispose to or predict long-term renal function loss in fPE women remains unclear. Long-term follow-up studies should further unravel the underlying pathways and consequences of a high-normal GFR in fPE women. The fPE women within this cohort are currently being recruited for a second evaluation at 20 years postpartum.

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Disclosures

None.

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**Novelty and Significance**

**What Is New?**

- This is the first study on renal function in a large cohort of well-characterized former preeclamptic women compared with age-matched controls.
- We show a shift of estimated glomerular filtration rate distribution to the high-normal range accompanied by a slightly higher protein excretion in early-onset preeclamptic women 10 years postpartum.

**What Is Relevant?**

- Although our observations of subtle changes in renal function 10 years after preeclampsia do not have clinical implications, our findings do suggest that former preeclamptic women might be hyperfiltrating, which can contribute to the increased risk of end-stage kidney disease after preeclampsia.

**Summary**

We demonstrate subtle changes in renal function in former early-onset PE women 10 years postpartum, which is characterized by a high-normal estimated glomerular filtration rate and a slightly higher protein excretion.
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High-normal eGFR in early-onset preeclamptic women 10 years postpartum

Nina D. Paauw, MD¹, Jaap A. Joles, DVM PhD², José T. Drost, MD PhD³, Marianne C. Verhaar, MD PhD², Arie Franx, MD PhD¹, Gerjan Navis, MD PhD⁴, Angela H.E.M. Maas, MD PhD⁵ and A. Titia Lely, MD PhD¹

¹ Department of Obstetrics, Wilhelmina Children’s Hospital Birth Center, University Medical Center Utrecht, Utrecht, Netherlands; ²Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, Netherlands; ³Department of Cardiology, Isala Klinieken, Zwolle, Netherlands; ⁴Department of Nephrology, University Medical Center Groningen, Groningen, Netherlands; ⁵Department of Cardiology, Radboud University Medical Center, Nijmegen, Netherlands.

Corresponding author:

N.D. Paauw

Division Women and Baby

University Medical Centrum Utrecht

Postbus 85090, 3508 AB Utrecht, The Netherlands

Tel: +31 88 755 7526/ Fax: +31 88 755 5436

E-mail: n.d.paauw-2@umcutrecht.nl
Table S1. PREVFEM cohort with exclusion of participants with Diabetes Mellitus. Median eGFR in fHP and fPE (A) and unadjusted and adjusted odds ratio’s for fPE to have an eGFR > 110 ml/min/1.73m$^2$ (B).

<table>
<thead>
<tr>
<th></th>
<th>(A) Median eGFR</th>
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<tr>
<td></td>
<td>fHP</td>
<td>fPE</td>
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<tr>
<td>MDRD</td>
<td>95 (86-106)</td>
<td>97 (85-109)</td>
</tr>
<tr>
<td>CKD-epi</td>
<td>105 (94-111)</td>
<td>106 (93-113)</td>
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<table>
<thead>
<tr>
<th></th>
<th>(B) Unadjusted and adjusted odds ratio's</th>
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<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
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<tr>
<td>MDRD&gt;110 ml/min/1.73m$^2$</td>
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<td></td>
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<tr>
<td>Unadjusted</td>
<td>1.56 (1.06-2.27)</td>
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<tr>
<td>Adjusted for MAP</td>
<td>1.61 (1.09-2.39)</td>
<td>0.02</td>
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<tr>
<td>Adjusted for years postpartum</td>
<td>1.48 (1.00-2.19)</td>
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<tr>
<td>Adjusted for OC use</td>
<td>1.53 (1.04-2.25)</td>
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<td>Adjusted for years postpartum and OC use</td>
<td>1.45 (0.98-2.15)</td>
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<tr>
<td>CKD-epi&gt;110 ml/min/1.73m$^2$</td>
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<tr>
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<tr>
<td>Adjusted for years postpartum and OC use</td>
<td>1.16 (0.82-1.63)</td>
<td>0.40</td>
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Data are expressed as median (25th percentile - 75th percentile) or odds ratio’s (95% confidence intervals) with corresponding p-values. fHP: former healthy pregnant women; fPE: former preeclamptic women; MAP: mean arterial pressure; OC: oral contraceptive use.
Figure S1

MDRD

Skewness to right: fHP 1.53 ± 0.13 vs. fPE 0.44±0.13

CKD-epi

Skewness to the left: fHP -0.52 ± 0.14 vs. fPE -0.67±0.13

eGFR distributions in former healthy pregnant (fHP) and former preeclamptic (fPE) women. Gaussian fits are indicated by solid lines.