Course of preeclamptic glomerular injury after delivery


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Hladunewich MA, Myers BD, Derby GC, Blouch KL, Druzin ML, Deen WM, Naimark DM, Lafayette RA. Course of preeclamptic glomerular injury after delivery. Am J Physiol Renal Physiol 294: F614–F620, 2008. First published January 16, 2008; doi:10.1152/ajprenal.00470.2007.—We evaluated the early postpartum recovery of glomerular function over 4 wk in 57 women with preeclampsia. We used physiological techniques to measure glomerular filtration rate (GFR), renal plasma flow, and oncocotic pressure ($\pi_a$) and computed a value for the two-kidney ultrafiltration coefficient ($K_t$). Compared with healthy, postpartum controls, GFR was depressed by 40% on postpartum day 1, but by only 19% and 8% in the second and fourth postpartum weeks, respectively. Hypofiltration was attributable solely to depression, at corresponding postpartum times, of $K_t$ by 55%, 30%, and 18%, respectively. Improvement in glomerular filtration capacity was accompanied by recovery of hypertension to near-normal levels and significant improvement in albuminuria. We conclude that the functional manifestations of the glomerular endothelial injury of preeclampsia largely resolve within the first postpartum month.

glomerular filtration rate; ultrafiltration coefficient; postpartum recovery

AFFECTING 5–7% of pregnancies, preeclampsia remains a leading cause of maternal and fetal morbidity and mortality. Because the primary target of injury in preeclampsia is the glomerular endothelial cell, affected patients invariably present with depression of the glomerular filtration rate (GFR), proteinuria, and hypertension. We previously (13) evaluated glomerular morphology immediately after delivery. We demonstrated severe endothelial cell swelling with diminished size and density of the endothelial fenestrae, along with mesangial cell interposition and subendothelial fibrinoid deposits. These findings were computed to lower glomerular filtration capacity sufficiently to account for the observed depression of GFR by 40% (13).

Despite the profound alterations in glomerular morphology, clinical recovery is usually rapid after delivery of the placenta. However, few detailed physiological evaluations of preeclampsia have been undertaken in the postpartum period. The characteristic glomerular pathological lesion has been reported to improve within days after delivery (21). Although complete recovery can occasionally require in excess of 6 mo, the majority of cases demonstrate complete resolution of the renal pathology within 3 mo (25). With the exception of those women with persistent postpartum hypertension, GFR and proteinuria also normalize over several months (18, 32–34).

In the present study, we have employed precise physiological techniques to evaluate the postpartum course of the GFR and its determinants in women with preeclampsia. We combined our physiological findings with mathematical modeling to estimate glomerular ultrafiltration capacity. We observed a profound initial injury, which improved significantly after 4 wk.

METHODS

Patient population. This paper represents a cross-sectional analysis of two previous study protocols, the results of which have already been published elsewhere (10, 11, 13). Women selected for the studies were diagnosed with preeclampsia in the second half of pregnancy (1, 15). All participants were patients admitted to Stanford University Medical Center. Inclusion criteria were 1) an elevation of blood pressure to levels in excess of 140 mmHg systolic over 90 mmHg diastolic and 2) proteinuria determined by a urine dipstick value $\geq 2$+ or quantitated at $\geq 0.5$ g either per gram of creatinine or in a 24-h urine collection. Women with a history of underlying renal disease defined as prepregnancy azotemia (serum creatinine $\geq 1.2$ mg/dl) or proteinuria were excluded.

Fifty-seven women with preeclampsia consented to participate. Twelve women were studied on postpartum day 1, of whom seven returned for evaluation in the fourth postpartum week (group 1). These women had a morphometric analysis of a kidney biopsy that was performed immediately postpartum along with a physiological evaluation of glomerular function that has been reported previously (13). A second group of 45 preeclamptic women were studied on postpartum day 3, of which 39 returned for a second study during the second postpartum week (group 2). These women participated in a randomized controlled trial of l-arginine vs. placebo that has also been reported elsewhere (10). Because no effect of l-arginine was noted, the placebo and l-arginine groups were combined for the purpose of this evaluation. Thirty-four healthy gravid women provided control values for the postpartum values of interest (11). These women were randomly selected from the obstetric ward or responded to advertisements posted throughout the hospital. Thirty-nine healthy female volunteers of reproductive age (20–48 yr) provided control values for the corresponding studies of preeclampsia on day 25, by which time the hyperfiltration accompanying a normal gravid state has been restored to nongravid levels (31). Each patient consented to undergo a detailed study of glomerular function that was approved by the Institutional Review Board at Stanford University. While measurements occurred during separate study protocols, all studies were completed or supervised by a single expert nurse, ensuring consistency in the clearance methodology.

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Physiological evaluation. All subjects had blood drawn for a determination of plasma oncotic pressure ($\pi_A$), hematocrit (Hct), and creatinine. A urine sample was collected for determination of albumin and creatinine concentrations. A bladder catheter permitted accurate urine collections in all day 1 and some day 3 studies. In the remainder of studies, urine was collected by spontaneous voiding after diuresis had been established with an oral water load (10–15 ml/kg). A priming dose of inulin (50 mg/kg) and p-aminohippuric acid (PAH, 12 mg/kg) was then administered. Thereafter, inulin and PAH were given by continuous infusion to maintain plasma levels constant at ~20 and 1.5 mg/dl, respectively.

The bladder was emptied 60 min after the priming infusion, and blood pressure was determined by Dynamap (Johnson & Johnson, Tampa, FL). Four timed urine collections were then made, each of which was bracketed by a blood sample drawn from a peripheral vein. The GFR was expressed as the average value for the four timed inulin clearances. The rate of renal plasma flow (Q$_A$) was estimated by dividing the corresponding clearance of PAH by an assumed renal arteriovenous extraction ratio for PAH. We showed previously (3) that reductions of GFR and peritubular capillary protein concentration exert an additive effect to lower the PAH extraction ratio in patients with glomerular disease. From the relationship observed in that study between the PAH extraction ratio and GFR, we have assigned the following values to the subjects of the present study: 0.9 for healthy controls, 0.8 for patients with nephrotic range proteinuria and a GFR >80 ml·min$^{-1}$·1.73 m$^{-2}$, and 0.7 for patients with proteinuria and a GFR depressed below 80 ml·min$^{-1}$·1.73 m$^{-2}$. Both the GFR and Q$_A$ were adjusted for body surface area, using the prepregnancy weight as reported by the patient and confirmed by review of the medical record of the first obstetric visit. Renal blood flow was calculated by dividing Q$_A$ by (1 – Hct), and renal vascular resistance (RVR) was derived by dividing mean arterial pressure (MAP) by renal blood flow.

Inulin and PAH concentrations were determined with colorimetric methods using a Technicon Auto Analyzer II (3). Plasma oncotic pressure was measured directly with a Wescor (Wescor, Logan, UT). Urinary albumin concentration was determined by rate nephelometry, and the simultaneous urinary creatinine concentration was determined with a Beckman creatinine analyzer to provide a urinary albumin-to-creatinine ratio (A/C).

The healthy subjects completing a normal pregnancy provided control values for all of the determinations performed in the experimental preeclamptic groups, with the exception of those on postpartum day 3. Although blood and urine were sampled, the detailed physiological evaluation could not be undertaken because most women completing a normal uncomplicated pregnancy are discharged from hospital on postpartum day 3. We did not recruit women who had a healthy pregnancy to complete a postpartum day 25 assessment. Because GFR has been shown to return to normal, nongravid values in the majority of women by the fourth postpartum week (31), we utilized 39 nongravid healthy women of reproductive age (18–45 yr) to provide control values for day 25.

Theoretical analysis. A mathematical model for the glomerular filtration of water (6) was used to calculate the two-kidney ultrafiltration coefficient ($K_f$), which is defined in this study as the product of glomerular hydraulic permeability and the total filtration surface area of all glomerular capillaries in the two human kidneys. The input values for the model included the measured values of GFR, Q$_A$, and $\pi_A$, the oncotic pressure of plasma entering the afferent glomerular arteriole, as well as an assumed value for the glomerular transcapillary hydraulic pressure difference ($\Delta P$). The latter quantity cannot be directly measured in humans. We accordingly used and reported (5) an indirect technique to estimate that $\Delta P$ approximates 40 mmHg in the healthy human kidney and used this approximation in our gravid and nongravid controls, with the exception of the second postpartum week. We recently reported (11) that an elevation of $\Delta P$ by ~2 mmHg may be necessary to explain the level of hyperfiltration observed in healthy mothers in the second postpartum week. We thus used $\Delta P = 42$ mmHg as well as $\Delta P = 40$ mmHg to estimate a likely range for $K_f$ in our healthy gravid control group in the second postpartum week. Finally, we made the conservative assumption that 20–30% of the increment in arterial pressure is likely transmitted into glomerular capillaries of hypertensive preeclamptic patients and that $\Delta P$ in preeclampsia is thus elevated to 45 mmHg during the first two postpartum weeks.

We then used the measured values of GFR, $Q_A$, and $\pi_A$, and the aforementioned assumed values for $\Delta P$ to compute a corresponding range of values for whole kidney $K_f$ with a modification of the model of ultrafiltration of Deen et al. (6). In this modification, it is assumed that, for the range of plasma protein concentrations observed in humans, the plasma oncotic pressure ($\pi$) is approximately proportional to the total protein concentration (C), an assumption that is consistent with an earlier study from our laboratory (4). To the extent that protein loss is negligible, conservation of mass gives $C_p = C_l/(1 - FF)$, where subscripts E and A refer to efferent and afferent arterioles, respectively, and FF is filtration fraction. If, in addition, $\pi = \alpha C$, where $\alpha$ is a constant for a given subject or sample, then it is also true that $\pi_p = \pi_A/(1 - FF)$. If this is the case, then $K_f$ can be estimated without knowing the value of $\alpha$. With $\pi A$ linear function of C and $\Delta P$ a constant, a derivation like that in Deen et al. (6) leads to:

$$K_f = \frac{Q_A}{\Delta P} \ln \left( \frac{1}{1 - \frac{A}{FF}} \right)$$

where $A = \pi A/\Delta P$. For whole kidney inputs, $Q_A$ is the renal plasma flow rate and FF = GFR/$Q_A$. Thus the procedure for estimating $K_f$ is 1) assume a value of 40–42 or 45 mmHg for $\Delta P$ in normotensive controls and hypertensive preeclamptic patients, respectively, 2) calculate $A$ from $\Delta P$ and the measured $\pi_A$, and 3) calculate $K_f$ from $A$, the measured FF, the measured $Q_A$, and $\Delta P$.

Statistical analysis. For continuous variables, either a Student’s $t$-test or the Wilcoxon rank-sum test was utilized to assess the significance of differences observed between the preeclamptic patients and healthy control subjects at the time points of interest. A Student’s $t$-test of the null hypothesis of the zero slope was determined by 10.2235 on October 13, 2017 http://ajprenal.physiology.org/ Downloaded from http://ajprenal.physiology.org/ by 10.2235 on October 13, 2017
Prominent clinical features of preeclampsia are compared with control values during the corresponding postpartum time points in Table 2. Day 1 mean MAP and RVR exceeded corresponding control values by 23 mmHg and 39 mmHg·min⁻¹·mmHg⁻¹, respectively (P < 0.05). Reflecting the volume expansion and hemodilution at the end of pregnancy, Hct and serum albumin levels were depressed in both populations (Table 2). Glomerular injury in preeclampsia was reflected on day 1 by significant elevation in serum creatinine, albeit within the normal range (0.85 ± 0.22 vs. 0.60 ± 0.10 mg/dl; P < 0.001) and persistent macroalbuminuria (Table 2).

Hypertension and elevated renovascular pressure persisted in preeclamptic subjects during postpartum weeks 1 and 2 but normalized by postpartum week 4 (Table 2). The slope of MAP was −1.1 mmHg/day (P < 0.001). Serum albumin and Hct increased in parallel in control subjects, reflecting reversal of the hemodilution (Table 2). Reflecting resolution of the glomerular injury, median albuminuria in preeclamptic patients declined from 687 mg/g creatinine on day 1 to 306 and 213 mg/g creatinine in postpartum weeks 2 and 4, respectively (Table 2). The slope for improvement in A/C was −68 mg/g of creatinine per day (P < 0.001). A normalization of the serum creatinine in preeclamptic subjects by postpartum week 2 to 0.64 ± 0.18 mg/dl points to measurable improvement in GFR by this time.

**Determinants of GFR.** Glomerular pressures and flows are summarized in Table 3. Compared with the marked hyperfiltration observed in healthy control subjects on postpartum day 1, the corresponding GFR in preeclamptic subjects was substantially depressed, 149 ± 33 vs. 89 ± 25 ml·min⁻¹·1.73 m⁻², respectively (P < 0.001). Neither renal plasma flow nor πₐ on postpartum day 1 differed significantly between preeclamptic patients and control subjects. Using our assumed values for ΔP, we compute that GFR depression in preeclamptic subjects owes exclusively to a marked depression of Kᵣ to 3.46 ± 1.26 ml·min⁻¹·mmHg⁻¹ vs. the control value of 7.66 ± 2.08 ml·min⁻¹·mmHg⁻¹ (Table 3, Fig. 1). This profound degree of Kᵣ depression could not be appreciated by evaluation of the serum creatinine, which is classically the clinical parameter followed (Table 2, Fig. 2). Although statistically significantly different, the serum creatinine remained in the normal range for both groups, with a value of 0.85 ± 0.22 mg/dl in preeclamptic patients and 0.60 ± 0.10 mg/dl in healthy gravid control subjects (Table 2).

Opposite trends for GFR between postpartum week 1 and week 2 were observed in the preeclamptic and control groups (Fig. 1). GFR fell significantly to 125 ± 29 ml·min⁻¹·1.73 m⁻² in controls by the second postpartum week. This was attributable to a rapid increase to normal levels of πₐ between week 1 and week 2 as postpartum volume contraction and hemoconcentration ensued (Table 3, Fig. 1). Assuming that ΔP increases by 2 mmHg in response to the volume contraction, the computed week 2 Kᵣ does not differ from day 1 values, indicating that this modest increase in ΔP is necessary to offset the increase in πₐ and explaining the persistently high GFR of 125 ± 29 ml·min⁻¹·1.73 m⁻² at this time. An alternative explanation for the high GFR is that ΔP remained at 40 mmHg but Kᵣ increased by 40% over baseline levels to 11.61 ± 5.29 ml·min⁻¹·mmHg⁻¹, a phenomenon that seems to us to be implausible.

In contrast to control subjects, the GFR tended to increase over day 1 levels in postpartum week 2 in preeclamptic subjects (89 ± 25 to 105 ± 31 ml·min⁻¹·1.73 m⁻²), despite an average increase in the opposing oncotic pressure, πₐ, comparable to that observed in control subjects by 5.6 vs. 7.1 mmHg, respectively (Table 3). An increase in computed Kᵣ to 5.90 ± 2.87 ml·min⁻¹·mmHg⁻¹ at this time appears to account for the higher GFR in preeclampsia (Table 2, Fig. 1).

GFR, renal plasma flow, and πₐ in our week 4 preeclamptic subjects were all numerically, but not significantly, lower than in nongravid control subjects. That the endothelial injury had not healed completely is suggested by the persistence of Kᵣ.

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**Table 2. Clinical characteristics**

<table>
<thead>
<tr>
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<th>Week 1</th>
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<td></td>
<td>Day 1</td>
<td>Day 3</td>
<td>Week 2</td>
<td>Week 4</td>
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<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>104±12</td>
<td>103±12</td>
<td>97±12</td>
<td>86±7</td>
</tr>
<tr>
<td>Control</td>
<td>81±6*</td>
<td>79±7*</td>
<td>81±8*</td>
<td>83±8</td>
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<tr>
<td>RVR, mmHg·min⁻¹·1⁻¹</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>131±44</td>
<td>161±68</td>
<td>151±48</td>
<td>127±23</td>
</tr>
<tr>
<td>Control</td>
<td>92±23*</td>
<td>NA</td>
<td>105±23*</td>
<td>104±34</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>0.85±0.22</td>
<td>0.62±0.19</td>
<td>0.64±0.18</td>
<td>0.67±0.10</td>
</tr>
<tr>
<td>Control</td>
<td>0.60±0.10*</td>
<td>0.49±0.11*</td>
<td>0.53±0.09*</td>
<td>0.76±0.11*</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
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<td></td>
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<tr>
<td>PET</td>
<td>1.9±0.2</td>
<td>2.1±0.4</td>
<td>2.8±0.5</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>Control</td>
<td>2.0±0.2</td>
<td>2.5±0.2*</td>
<td>3.2±0.3*</td>
<td>3.9±0.5*</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>34±3</td>
<td>31±4</td>
<td>32±4</td>
<td>34±3</td>
</tr>
<tr>
<td>Control</td>
<td>31±3*</td>
<td>32±3</td>
<td>37±3*</td>
<td>37±2*</td>
</tr>
<tr>
<td>Urine A/C, mg/g Cr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>687 (211–2,145)</td>
<td>575 (310–1,109)</td>
<td>306 (99–446)</td>
<td>213 (105–2,527)</td>
</tr>
<tr>
<td>Control</td>
<td>22 (17–80)*</td>
<td>101 (51–143)*</td>
<td>21 (13–47)*</td>
<td>5 (4–7)*</td>
</tr>
</tbody>
</table>

Values are means ± SD and medians (95% confidence interval) for postpartum weeks 1, 2, and 4. Twelve preeclamptic (PET) patients were studied on day 1, of which 7 returned for a second evaluation during week 4 (group 1); 45 PET patients were studied on day 3, of which 39 returned for a second evaluation during week 2 (group 2). MAP, mean arterial pressure; RVR, renal vascular resistance; A/C, albumin-to-creatinine ratio; NA, not available. *P < 0.05, gravid control subjects compared with PET patients for corresponding day.
Table 3. Filtration dynamics

<table>
<thead>
<tr>
<th>GFR, ml·min⁻¹·1.73 m⁻²</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 4</td>
</tr>
<tr>
<td>PET</td>
<td>89±25</td>
<td>114±33</td>
<td>105±31</td>
</tr>
<tr>
<td>Control</td>
<td>149±33*</td>
<td>NA</td>
<td>125±29*</td>
</tr>
<tr>
<td>Qₐ, ml·min⁻¹·1.73 m⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>610±212</td>
<td>498±168</td>
<td>461±117</td>
</tr>
<tr>
<td>Control</td>
<td>624±108</td>
<td>NA</td>
<td>660±140*</td>
</tr>
<tr>
<td>FF</td>
<td>0.16±0.05</td>
<td>0.24±0.07</td>
<td>0.23±0.05</td>
</tr>
<tr>
<td>Control</td>
<td>0.24±0.05*</td>
<td>NA</td>
<td>0.25±0.06</td>
</tr>
<tr>
<td>πₐ, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>16.9±2.7</td>
<td>18.8±2.7</td>
<td>22.5±3.5</td>
</tr>
<tr>
<td>Control</td>
<td>17.6±1.3</td>
<td>NA</td>
<td>24.7±1.7*</td>
</tr>
<tr>
<td>Kₐ, ml·min⁻¹·mmHg⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>3.46±1.26</td>
<td>4.94±1.76</td>
<td>5.90±2.87</td>
</tr>
<tr>
<td>Control</td>
<td>7.66±2.08*</td>
<td>NA</td>
<td>11.61±5.29 to 9.55±3.74*</td>
</tr>
</tbody>
</table>

Values are means ± SD for postpartum weeks 1, 2, and 4. Twelve PET patients were studied on day 1, of which 7 returned for a second evaluation during week 4 (group 1); 45 PET patients were studied on day 3, of which 39 returned for a second evaluation during week 2 (group 2). GFR, glomerular filtration rate; Qₐ, renal plasma flow; FF, filtration fraction; πₐ, oncotic pressure of blood entering the afferent arteriole; Kₐ, 2-kidney ultrafiltration coefficient calculated with a glomerular transcapillary hydraulic pressure difference (ΔP) of 40 mmHg, with the exception of a ΔP of 45 mmHg in week 1 PET patients and ΔP of 40 and 42 mmHg during postpartum week 2 in gravid control subjects. *P < 0.05; gravid control subjects compared with PET patients for corresponding day.

Depression, albeit of only modest severity at this late stage of the puerperium, on average 6.87 ± 1.36 vs. 8.39 ± 1.85 ml·min⁻¹·mmHg⁻¹ (P < 0.05; Table 3, Fig. 1). The slope for kᵣ improvement was 0.14 ml·min⁻¹·mmHg⁻¹ per day (P = 0.002).

Discussion

The glomerular injury of preeclampsia manifests as a clinical triad, namely, hypertension, proteinuria, and a loss of intrinsic filtration capacity that lowers the GFR. Although we estimate that filtration capacity, as approximated by an ultrafiltration coefficient (kᵣ), is depressed by >50% at the end of pregnancy (postpartum day 1, Table 3), this phenomenon is not widely recognized by clinicians. This is because GFR depression in clinical practice is identified by the presence of azotemia. The absence of overt azotemia (usually defined in women as serum creatinine >1.2 mg/dl) in preeclamptic mothers during postpartum weeks 1 and 2 obscured the extent to which GFR and computed kᵣ were depressed in these subjects compared with healthy gravid control subjects.

We examined glomerular structure and ultrastructure in those subjects of the present report who were studied on day 1. We undertook a morphometric analysis of transmission and scanning electron photomicrographs (13). We showed that reduced size and density of endothelial fenestrae, along with deposition of subendothelial fibrinoid, lowered the hydraulic permeability (k) of glomerular capillary walls. Simultaneously, swollen endothelial segments devoid of fenestrae and mesangial interposition limited the capillary surface area available for filtration (S) (13). From the product of S and k, we computed that single-nephron kᵣ was sufficiently lowered to account completely for the observed 40% reduction in measured GFR (13).

Changes in glomerular endothelial cells that are remarkably similar to those observed in preeclamptic humans have been induced in pregnant rats by injecting an adenovirus expressing soluble fms-like tyrosine kinase (sFlt-1), which will bind to vascular endothelial growth factor (VEGF), preventing its interaction with the fms-like tyrosine kinase receptor (Flt-1). The glomerular injury further resembled human preeclampsia, in that it was associated with hypertension and albuminuria (17). Placental upregulation of sFlt-1 has been demonstrated in women with preeclampsia, and this excess is thought to inhibit VEGF receptors, which are present on glomerular endothelial cells and podocytes. It has been proposed that VEGF signaling is key in maintaining the integrity of the glomerular filtration barrier, and that dysregulation of the paracrine and autocrine pathways of VEGF leads to the glomerular barrier dysfunction noted in preeclampsia (9). Restoration of the normal balance of angiogenic factors that occurs after delivery of the placenta likely promotes rapid endothelial cell healing, as noted in our patients with preeclampsia. A previous study inferred from sieving curves of uncharged dextran macromolecules of graded size that kᵣ was restored to normal after the fifth postpartum month (18).

In the present study, we have attempted to chart the course of preeclamptic glomerular injury immediately after delivery of the fetus and, more specifically, of the placenta, in which sFlt-1 has been shown to be markedly upregulated (17). This was a cross-sectional analysis that included two groups of preeclamptic patients studied during the puerperium: one group was studied on day 1 and during the fourth postpartum week, and the second group was studied on day 3 and during the second postpartum week. Whereas we would have preferred to study these time points longitudinally in the same mothers, four serial clearance studies are too demanding for most postpartum mothers. Instead we have had to compromise by performing a cross-sectional analysis of the two aforementioned groups of subjects.

We estimated kᵣ and its role in determining the prevailing GFR. Ideally, we could have used the hydrodynamic model of Drumond et al. (8) to accurately estimate single-nephron kᵣ from a morphometric analysis of glomeruli obtained by needle biopsy. However, renal biopsy is an invasive procedure that is not without risk, and thus difficult to justify purely for research.
purposes in a large population of preeclamptic mothers. Instead we used physiological techniques to determine GFR and its hemodynamic determinants and then computed two-kidney $K_f$ with a modification of the mathematical model of glomerular ultrafiltration of Deen et al. (6). Whereas $\pi_A$ and renal plasma flow ($Q_A$) can be determined with reasonable precision in the human kidney (3, 4), $\Delta P$ cannot be measured because of the inaccessibility of humanglomeruli.

We previously (11) used an indirect method to estimate $\Delta P$ in healthy mothers in the postpartum period. We performed a morphometric analysis of glomerular ultrastructure in living kidney donors who were females in their reproductive years and computed a value for single-nephron $K_f$ (7). We multiplied the latter by a reported mean number of glomeruli of $1.4 \times 10^6$ at autopsy in women of reproductive age with no history or evidence of a renal disease (23). This product provides an estimate of two-kidney $K_f$. We then modified the ultrafiltration model originally described by Deen and colleagues (26) to compute $\Delta P$ in these living kidney donors from measured GFR, $Q_A$, $\pi_A$, and the foregoing estimate of two-kidney $K_f$.

Because there is no reabsorption during axial flow along glomerular capillaries, the corresponding lower bound for $\Delta P$ cannot be less than efferent oncotic pressure ($\pi_E$), which we have estimated from $\pi_A$ and the filtration fraction to be 30–33 mmHg in healthy subjects (4). However, we have repeatedly shown GFR to remain constant during hypervolemia-induced elevations of $Q_A$ by 15–25% (16, 19, 29). Such independence of GFR from $Q_A$ is typical of filtration pressure dysequilibrium (6), from which we can infer that $\Delta P$ is substantially higher than $\pi_E$ and thus consistent with an estimate of 40 mmHg. We accordingly selected a $\Delta P$ of 40 mmHg as the best-guess value for $\Delta P$ in our gravid day 1 and our nongravid week 4 control subjects. In our week 2 control subjects, however, hyperfiltration persisted despite a steep increase in $\pi_A$ associated with volume contraction and hemoconcentration. An increase in $\Delta P$ to 42 mmHg accounts best for the observed level of hyperfiltration (11). We accordingly used a range of $\Delta P$ from 40 to 42 mmHg as the best-guess value for $\Delta P$ in our gravid control groups between postpartum day 1 and week 2.

Assuming that $\Delta P$ increased from 40 to 42 mmHg in our gravid control groups between postpartum day 1 and week 2, there was no significant change in $K_f$, 7.66 ± 0.208 vs. 9.55 ± 3.74 ml/min⁻¹·mmHg⁻¹, respectively. The $K_f$ in nongravid controls (representing the latter part of the first postpartum month) was also similar, 8.39 ± 1.85 ml/min⁻¹·mmHg⁻¹ (Table 3). In contrast, $K_f$ in preeclampsia increased significantly between postpartum day 1 and week 2 from 3.46 ± 1.26 to 5.90 ± 2.87 ml/min⁻¹·mmHg⁻¹. This permitted GFR to rise above the day 1 level of 89 ± 25 ml/min⁻¹·1.73 m⁻² to
105 ± 31 ml·min⁻¹·1.73 m⁻² in week 2 despite the substantial increase of corresponding values of $\pi_A$, the pressure that opposes the formation of filtrate, from 16.9 ± 2.7 to 22.5 ± 3.5 mmHg. The $K_I$ continued to increase in the postpartum week 4 group, entering the range observed in nongravid control subjects (Fig. 1, Table 3). This persistent improvement of $K_I$ in preeclampsia during the first postpartum month parallels that of albuminuria and blood pressure (Table 2). That improving $K_I$ reflects recovery of the injured glomerular endothelial cell and parallels pathological observations that the severity of endotheliosis correlates inversely with the postpartum day on which the biopsy was performed (21, 24, 25).

The substantial improvement in filtration capacity in the early postpartum period is not usually identified clinically. This is partly because a steep, simultaneous increase in $\pi_A$ leaves GFR relatively unchanged (Table 3, Fig. 1). More pertinent to the clinical situation, however, is that the inverse hyperbolic relationship between serum creatinine and GFR is blunted in the elevated range of the latter that is associated with pregnancy (Fig. 2). The range for serum creatinine (0.56 – 0.96 mg/dl) in our healthy nongravid control subjects is illustrated by the two parallel dashed lines in Fig. 2. As shown, a substantial minority of preeclamptic mothers exceed this range. In fact, serum creatinine exceeded the normal nongravid range in only those subjects whose GFR was depressed by >50% below the gravid control mean of 149 ml·min⁻¹·1.73 m⁻², and the highest value observed among our preeclamptic subjects was only 1.4 mg/dl.

Although we observed marked improvement in MAP, filtration capacity, and albuminuria during the first postpartum month, complete healing was not achieved as judged by persistent microalbuminuria and modest depression of $K_I$. In most cases, complete resolution has been reported to occur over a period of 3–6 mo, but full recovery has been found in some cases of preeclampsia to require in excess of 12 mo (14, 22, 23). Studies suggest that the preeclamptic glomerular injury can become chronic. One study noted that 42% of women with a history of preeclampsia exhibited microalbuminuria and a mean blood pressure of 133/87 mmHg 3–5 yr postpartum compared with 118/73 mmHg in a control group of women with no history of preeclampsia (2). Others have also found evidence of microalbuminuria even longer after delivery, with rates of ~20% among formerly preeclamptic women (20, 28). Women with a history of preeclampsia are at increased risk of cardiovascular death compared with healthy gravid control subjects (12, 27). Whether incomplete healing of the preeclamptic glomerular endothelial injury plays a roll in this risk is unknown.

We conclude that the glomerular endothelial injury of preeclampsia results in a profound reduction in ultrafiltration capacity, which improves markedly by the latter part of the first postpartum month. Because of simultaneous changes in filtration pressure, largely a consequence of a brisk increase in glomerular oncotic pressure, GFR does not increase in parallel. The inadequacy of serum creatinine as a clinical surrogate for filtration capacity under postpartum conditions obscures the extent of initial impairment and subsequent improvement of $K_I$ during recovery from preeclampsia in the first postpartum month.

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