The Dynamics of Glomerular Filtration after Caesarean Section

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Abstract. The objective of this study was to determine whether the glomerular hyperfiltration of pregnancy is maintained even after Caesarean section and, if so, to define the responsible hemodynamics. The dynamics of glomerular filtration were evaluated in 12 healthy women who had just completed an uncomplicated pregnancy and were delivered by Caesarean section. Age-matched but non-gravid female volunteers (n = 22) served as control subjects. GFR in postpartum women was elevated above control values by 41%; 149 ± 10 versus 106 ± 3 ml/min per 1.73 m², respectively (P < 0.001). In contrast, corresponding renal plasma flow was the same in the two groups, such that the postpartum filtration fraction was significantly elevated by 20%. Computation of glomerular intracapillary oncostic pressure (πGC) from knowledge of plasma oncostic pressure and the filtration fraction revealed this quantity to be significantly reduced in postpartum women, 20.6 ± 1.7 versus 26.1 ± 2.0 mmHg in control subjects (P < 0.001). A theoretical analysis of glomerular ultrafiltration suggests that depression of πGC, the force opposing the formation of filtrate, is predominantly or uniquely responsible for the observed postpartum hyperfiltration.

Human pregnancy results in a substantial elevation of the GFR. Serial observations suggest that GFR rises progressively to a peak level in mid-pregnancy, and is maintained constant thereafter for the duration of the pregnancy (1–6). On average, GFR during the second half of pregnancy has been shown to be elevated above non-gravid levels by 40 to 50%. Information regarding GFR during the early postpartum period is scant, but several serial studies have shown that it is restored to the non-gravid range some 2 to 3 mo after delivery.

The purposes of the present study were twofold. One was to determine whether glomerular hyperfiltration persists in the immediate wake of pregnancy. Patients completing Caesarean section were chosen for study because they had in-dwelling bladder catheters in place facilitating precise measurement of renal function. The second was to evaluate how alterations in its underlying determinants influence the GFR that prevails at this time.

Materials and Methods

Patient Population

The subjects of our study were 12 healthy women who had completed an uncomplicated pregnancy. These patients underwent elective Caesarean section for an indication of prior Caesarean or breech presentation. They had undergone epidural anesthesia. Each consented to undergo a study of renal function that had been approved by the Institutional Review Board at Stanford University. It was conducted within a few hours of the end of pregnancy. In each case, the gestation had reached full-term with a duration that averaged 39 ± 1 wk (mean ± SD). Twenty-two healthy and non-gravid female volunteers served as control subjects. The experimental and control groups were matched for age averaging 34 ± 2 and 30 ± 1 yr, respectively (P = NS). Renal disease, hypertension, and diabetes mellitus were excluded in each member of both groups by history, clinical examination, and routine laboratory evaluation.

Physiologic Evaluation

Postpartum mothers were studied in the recumbent position immediately after being returned to the obstetrical ward from the operating suite. They were awake and cooperative and had not begun breastfeeding. On average, the priming doses of inulin and para-aminohippurate (PAH) (50 and 12 ml/kg, respectively) were administered 4.3 ± 1.1 h after delivery. These were followed by a constant infusion of each marker, so as to maintain plasma levels of inulin and PAH constant at approximately 20 and 1.5 mg/dl, respectively. After a 60-min period of equilibration, BP was determined by Dinamap (Johnson & Johnson, Tampa, FL), and blood was drawn for determination of plasma oncostic pressure and for serum concentrations of albumin and clearance markers. Four 30-min collections of urine were then made via an in-dwelling Foley bladder catheter (Bard, Inc., Covington, GA), thereby permitting accurate collections of urine uncontaminated by lochia. Plasma was sampled so as to bracket each urine collection. Clearances of inulin and PAH were determined by dividing the urinary excretion rate of each marker by its plasma concentration. GFR was expressed as the average value for the four timed inulin clearances. The rate of renal plasma flow (RPF) was estimated by dividing the corresponding clearance for PAH by an assumed renal arteriovenous extraction ratio for PAH of 0.9 (7). The control group was studied in a General Clinical Research Center using a protocol that was identical with only one exception. Control subjects

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were not catheterized, and voided timed urine samples spontaneously during a state of water diuresis.

Inulin and PAH were assayed using an autoanalyzer technique. The fructose-specific reagent resorcinol was used to assay inulin and Marshal reagent was used to assay PAH. The oncotic pressure in venous plasma was taken to be the same as that in plasma entering the glomerular tuft (πA) and was measured in a Wescor 4400 colloid osmometer (Wescor, Inc., Logan, UT) as described previously (8). The corresponding albumin concentration in serum was determined by rate nephelometry (8).

Theoretical Analysis

The relationship between GFR and its determinants was assessed by using the following equation:

\[ \text{GFR} = (\Delta P - \pi_{GC}) \times K_f \]  

(1)

where \( \Delta P \) is the transcapillary hydraulic pressure difference, \( \pi_{GC} \) is the mean glomerular intracapillary oncotic pressure, and \( K_f \) is the glomerular ultrafiltration coefficient, i.e., the product of hydraulic permeability and filtration surface area. To compute \( \pi_{GC} \), we first calculated the oncotic pressure of plasma entering the efferent arteriole from the glomerular tuft (\( \pi_e \)).

\[ \pi_e = \pi_A / (1 - \text{FF}) \]  

(2)

where \( \pi_A \) is afferent oncotic pressure, and FF is the filtration fraction. Equation 2 assumes that oncotic pressure rises linearly during axial plasma flow along the glomerular capillary loops, an assumption that we have shown previously to be accurate to within 0.5 mmHg (8). We then calculated \( \pi_{GC} \) as the mean of \( \pi_A \) and \( \pi_e \) (8).

We next used the mathematical model of glomerular ultrafiltration of Deen et al. to calculate the glomerular ultrafiltration coefficient \( K_f \) (9). Three of the input values required by the model are GFR, RPF, and \( \pi_A \). The fourth and remaining input value is \( \Delta P \), which cannot be directly measured in humans. Using indirect methods, however, it has been estimated that \( \Delta P \) in humans approximates 40 mmHg (10–12), and this value was assumed to apply to our healthy control subjects. Micropuncture studies in the rat suggest that \( \Delta P \) remains unchanged during pregnancy (13–16), leading us to assign a \( \Delta P \) value of 40 mmHg also to our postpartum group. However, to allow for the species difference, and to take into account the effect of possible variations in \( \Delta P \) on computed \( K_f \) at the end of human pregnancy, we also performed a sensitivity analysis. We used a 10 mmHg range of values for \( \Delta P \) from 35 to 45 mmHg as input values, so as to compute a range of values for \( K_f \) given the measured values of GFR, RPF and \( \pi_A \).

Statistical Analyses

All results are expressed as the mean ± SD. Unpaired t test was used to evaluate the significance of differences between the postpartum and non-gravid control groups.

### Results

Glorifieral flows and pressures are summarized in Table 1. The GFR in postpartum subjects was significantly elevated, exceeding corresponding control values by 41%, on average, 149 ± 34 versus 106 ± 15 ml/min per 1.73 m², respectively (\( P < 0.001 \)) (Table 1). Not shown in Table 1 is that a reciprocal depression of the serum creatinine level also reached significance, 0.60 ± 0.10 versus 0.79 ± 0.08 mg/dl, respectively (\( P = 0.01 \)). In contrast to the disparity in GFR, the value for RPF was essentially the same in the two groups (Table 1). Reflecting the selective elevation of GFR, the filtration fraction in the postpartum group was significantly elevated by 20% above control levels (Table 1).

In keeping with earlier reports (17–20), we found serum albumin concentration at the end of pregnancy to be below non-gravid levels, 2.3 ± 0.8 versus 3.8 ± 0.9 g/dl, respectively (\( P < 0.001 \)). Postpartum hypoalbuminemia was accompanied by a 5.6 mmHg reduction in measured oncotic pressure; such that \( \pi_A \) was only 17.6 ± 1.3 versus a control value of 23.2 ± 2.0 mmHg (\( P < 0.001 \)). Despite the elevated filtration fraction, the computed value for \( \pi_{GC} \) was also significantly lower in postpartum subjects than in gravid control subjects: 20.6 ± 1.7 versus 26.1 ± 2.0 mmHg (\( P < 0.001 \)). That this depression of the pressure opposing the formation of filtrate could be sufficient to explain the observed postpartum hyperfiltration is suggested by a consideration of the two remaining determinants of GFR, namely \( \Delta P \) and \( K_f \).

The average value for mean arterial pressure was numerically lower by 4 mmHg in the postpartum than in the control group (Table 1) (\( P = \text{NS} \)). It is thus not unlikely that corresponding glomerular capillary perfusion pressure, and hence postpartum \( \Delta P \), was also either slightly lower than or similar to control values (8,13–16,21). Assuming that the value for \( \Delta P \) was 40 mmHg in each group, we have used the measured values for GFR, RPF, and \( \pi_A \) to compute the two-kidney ultrafiltration coefficient (designated \( K_{f0} \) in Table 1). Calculated postpartum \( K_f \) was similar to the corresponding control value, tending if anything to be slightly lower; 8.6 ± 2.8 versus 10.0 ± 3.6 ml/(min · mmHg), respectively (\( P = \text{NS} \)). The effect on calculated \( K_f \) of variations in \( \Delta P \) in the postpartum group is illustrated in Figure 1. We first considered the possibility that the trend to lower mean arterial pressure at the end of pregnancy resulted in transmission of a lower pressure into glomerular capillaries with an ensuing 5 mmHg fall in \( \Delta P \) (to 35 mmHg; Figure 1, left column). As shown, this results in a reciprocal elevation of computed \( K_f \) to 12.8 ± 5.5 ml/(min · mmHg).

### Table 1. Filtration dynamicsa

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<th>( n )</th>
<th>GFR (ml/min per 1.73 m²)</th>
<th>RPF (ml/min per 1.73 m²)</th>
<th>FF (%)</th>
<th>MAP (mmHg)</th>
<th>( \pi_A ) (mmHg)</th>
<th>( \pi_{GC} ) (mmHg)</th>
<th>( K_{f0} ) (ml/min · mmHg)</th>
</tr>
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<tr>
<td>Postpartum</td>
<td>12</td>
<td>149 ± 34</td>
<td>560 ± 99</td>
<td>24 ± 5</td>
<td>81 ± 6</td>
<td>17.6 ± 1.3</td>
<td>20.6 ± 1.7</td>
<td>8.6 ± 2.8</td>
</tr>
<tr>
<td>Control subjects</td>
<td>22</td>
<td>106 ± 15</td>
<td>553 ± 128</td>
<td>20 ± 4</td>
<td>85 ± 9</td>
<td>23.2 ± 2.0</td>
<td>26.1 ± 2.0</td>
<td>10.0 ± 3.6</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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a RPF, renal plasma flow; FF, filtration fraction; MAP, mean arterial pressure; \( \pi_A \), afferent oncotic pressure; \( \pi_{GC} \), glomerular intracapillary oncotic pressure; \( K_{f0} \), two-kidney ultrafiltration coefficient.
would be offset by a reciprocal decline in computed hydraulic pressure difference \( (\Delta \mathbf{P}) \) beneath each bar, along with measured GFR, renal plasma flow (RPF) and afferent oncotic pressure \( (\pi_A) \). \(* P < 0.05 \) in the postpartum versus control group.

**Discussion**

The inulin clearance is widely regarded as the optimal method for the determination of GFR. Previous studies that have used this technique have demonstrated a constant elevation of GFR by 40 to 50\% during the second and third trimesters of pregnancy (1,2,4–6,21,22). The present study has extended this observation to show that hyperfiltration of similar magnitude is maintained early in the postpartum period. This latter finding is in accord with observations, based on the clearance of surrogate filtration markers (iohexol and creatinine), that hyperfiltration persists throughout the first postpartum week, but returns to normal non-gravid levels by the fourth postpartum week or beyond (23,24).

Our findings also provide insight into the mechanism by which postpartum GFR is elevated. Among the three determinants of GFR defined in Equation 1, they identify \( \pi_{GC} \) as the predominant factor contributing to the hyperfiltration. Micropuncture determinations in the pregnant rat (13,15) and an analysis of dextran sieving in pregnant humans (21), suggest that \( \Delta \mathbf{P} \) remains unaltered from non-gravid levels in these species. Provided that the same is true for postpartum \( \Delta \mathbf{P} \), our sensitivity analysis suggests that \( K_f \) too will be similar, and that depression of \( \pi_{GC} \) can in fact account on its own for the observed level of hyperfiltration (Figure 1, middle column). We cannot, of course, exclude the possibility that an increase in either \( \Delta \mathbf{P} \) or \( K_f \) also contributes to postpartum hyperfiltration. Given the measured values of GFR, RPF, and \( \pi_A \), however, a modest increase in \( \Delta \mathbf{P} \) is predicted to be offset by a reciprocal decline in \( K_f \) (Figure 1, right column). Similarly, a modest increase in \( K_f \) is predicted to be offset by a reciprocal decline in \( \Delta \mathbf{P} \) (Figure 1, left column). Thus, over a biologically probable range of values for \( \Delta \mathbf{P} \) at the end of pregnancy, depression of \( \pi_{GC} \), the force opposing the formation of filtrate, appears to be the most important, if not exclusive, determinant of hyperfiltration.

Serial hemodynamic evaluations during the course of human pregnancy have revealed disparate trends for GFR, RPF, and \( \pi_A \). GFR is constantly elevated throughout the second and third trimesters, whereas RPF peaks in the second trimester and then declines toward the “non-gravid” range in the third trimester (1,4,7,21). The present study extends these earlier findings, yet indicates a return in the early postpartum period to a value of RPF that is indistinguishable from that in healthy non-gravid control subjects. By necessity, our study coincided with a period during which postoperative influences, such as pain, could have lowered RPF by stimulating vasoconstrictor influences including enhanced sympathetic nervous traffic to the kidney and the release of vasopressin and other constrictor peptides (25,26). Another potential confounding factor is epidural anesthesia, which has been associated with small, albeit nonsignificant, reductions in RPF (27). Regardless of whether these anesthetic and postoperative influences contributed to the “normalization” of RPF to non-gravid levels, the fact remains that glomerular hyperperfusion cannot be invoked to explain the postpartum hyperfiltration that we observed. It is important to note that the apparent fall of RPF to normal levels in the early postpartum period is based on the assumption of normal PAH extraction. That this is likely to be the case is suggested by two earlier studies, in which normal PAH extraction ratios (range, 0.85 to 0.97) were directly measured during normal pregnancy (28,29).

\( \pi_A \), on the other hand, declines only modestly in the second trimester and then more profoundly in the third trimester (21,30), a phenomenon that has been attributed to progressive hypervolemia and hemodilution (17,19). Based on the recent serial findings of Roberts et al., we compute that an average 4.6 mmHg decline in measured \( \pi_A \) at 36 wk of gestation was accompanied by a 5.4 mmHg decline in \( \pi_{GC} \) (21). This depression of \( \pi_{GC} \) is similar in magnitude to that observed by us in the wake of delivery (Table 1), and is likely the predominant cause of hyperfiltration. On the other hand, the depression of measured \( \pi_A \) at 16 wk of gestation was only by 1.1 mmHg, and corresponding depression of computed \( \pi_{GC} \) by 1.5 mmHg. We note with interest that the GFR in the study of Roberts et al. was elevated above non-gravid levels by 48\%, both at 16 and 36 wk gestation. If one assumes that the large fall in \( \pi_{GC} \) was uniquely responsible for the hyperfiltration at 36 wk, it follows from the modest reduction in \( \pi_{GC} \) at 16 wk that elevation of one or both of the remaining determinants of GFR \( (\Delta \mathbf{P} \text{ or } K_f) \) must be invoked to explain the identical level of hyperfiltration early in the second trimester.

Baylis and her coworkers have used the micropuncture tech-
nique to elucidate the mechanism of hyperfiltration in the second trimester of pregnancy in the rat. As is the case in humans, hyperfiltration in the gravid rat was accompanied by a marked elevation of RPF, but only a small and insignificant reduction below control non-gravid levels of \( \pi_A \) (13,15). We estimate that \( \pi_{GC} \) declined by only 2 mmHg, a reduction that does not seem adequate to explain the 50% elevation of GFR. The \( \Delta P \) was also not different from non-gravid control levels. It thus seems reasonable to infer from Equation 1 that \( K_f \) must have increased to account for the hyperfiltration. Because both the gravid animals and the non-gravid control subjects in Baylis’ study were at filtration pressure equilibrium, a precise value for \( K_f \) could not be calculated. Nevertheless, at filtration pressure equilibrium, one would expect that an observed elevation of nephron plasma flow in pregnant rats would delay the axial rate of rise of oncotic pressure along the glomerular capillaries, thereby recruiting more surface area for filtration and elevating \( K_f \) (9).

A similar mechanism for \( K_f \) elevation in the second trimester of a human pregnancy seems unlikely, however. The hallmark of filtration pressure equilibrium is dependency of the GFR on the rate of plasma flow, a phenomenon that is prominent in the pregnant rat (13–16). In healthy humans, by contrast, we and others have consistently observed a lack of plasma flow dependency of GFR. Perturbations that substantially increase RPF have little or no effect on GFR (11,12,31,32). Thus, if \( K_f \) is indeed elevated in the second trimester of pregnancy, such elevation is unlikely to be attributable to recruitment of filtration surface area owing to enhanced glomerular perfusion, as appears to be the case in the rat.

We conclude that the magnitude of GFR elevation in the wake of delivery (by Caesarean section) is similar to that during the second and third trimesters of pregnancy. Knowledge of the expected normal range for GFR in the early postpartum period provides a standard against which to assess the extent of pregnancy-induced glomerular diseases, such as pre-eclampsia and the hemolytic uremic syndrome, which can complicate late pregnancy, and often persist, or even worsen after delivery. Such glomerular injury frequently requires termination of pregnancy by Caesarean section. It is thus noteworthy that our study reveals postpartum hyperfiltration to be of the same magnitude as reported during healthy pregnancy, notwithstanding the postoperative state. Our analysis of glomerular pressures and flows suggests that postpartum hyperfiltration, like that in the third trimester of pregnancy, is predominantly, if not uniquely, attributable to depression of \( \pi_{GC} \). In contrast, alterations in GFR determinants other than \( \pi_{GC} \) are required to explain the hyperfiltration that attends the second trimester of pregnancy.

Acknowledgments

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References