Fractional Excretion of Urea in Pre-eclampsia
A Clinical Observation

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Original Paper

Introduction. Pre-eclampsia is one of the leading causes of maternal and fetal mortality and morbidity. It occurs in 7% of all the pregnancies and accounts for 80% of the cases of pregnancy-induced hypertension. Diagnosis of pre-eclampsia in patients with pre-existing chronic kidney disease, proteinuria, and hypertension is a dilemma. The fractional excretion of urea has been described as a marker for renal perfusion. Since pre-eclampsia is associated with a marked decline in renal perfusion, we explored the utility of the fractional excretion of urea as a marker for pre-eclampsia.
Materials and Methods. Urine and serum chemistries were evaluated in 6 pregnant women with pre-eclampsia on their first visit, immediately prior to delivery, and postpartum. For each of these three measurements, the fractional excretion of urea was calculated and proteinuria was assessed by random urine protein-creatinine ratio or 24-hour urine protein studies.
Results. In patients diagnosed with pre-eclampsia, the fractional excretion of urea decreased substantially from higher values obtained during the 3rd trimester to values consistent with renal hypoperfusion (< 35%) just prior to delivery, and it rapidly normalized immediately after delivery.
Conclusions. Alterations in fractional excretion of urea, which suggest a decreased renal perfusion, may be a useful tool in supporting the diagnosis of preeclampsia.

INTRODUCTION

Pre-eclampsia is a syndrome characterized by the new onset of hypertension and proteinuria developing between 20 weeks gestation and 48 hours postpartum. Its etiology remains an enigma and symptoms vary widely.[1] It heralds eclampsia and is associated with significant short-term and long-term fetal and maternal mortality. Early diagnosis and appropriate management governs successful outcome.

Unfortunately the usual signs of pre-eclampsia, ie, proteinuria and hypertension, are the least specific diagnostic tools in patients who already have these conditions or in atypical presentations of pre-eclampsia.[2,3] While chronic kidney disease (CKD) is a risk factor for pre-eclampsia, the stress of pregnancy may also exacerbate or unmask underlying renal pathologies.[4] Although this differential diagnosis can be difficult, the ability to accurately distinguish between these two possibilities carries important therapeutic and prognostic implications. Prospects for women with moderate to severe CKD are grave, with 15% progressing to end-stage renal disease within 1 year and 90% having a problematic pregnancy.[5-7]

Research on diagnostic tests for pre-eclampsia has yielded certain serologic and urinary markers; however, these have yet to prove their worthiness

in routine clinical practice. At present, there is no single screening test that is considered reliable and cost-effective for predicting or diagnosing pre-eclampsia.[8,9] We have previously reported the utility of the fractional excretion of urea (FE_{urea}) as a marker of renal perfusion.[10] A value less than 35% is consistent with renal hypoperfusion. Since pre-eclampsia is associated with a significant increase in renal vascular resistance and renal hypoperfusion, we evaluated this marker as an indicator of pre-eclampsia. This study has been partially reported previously in the form of an abstract presented at the annual meeting of the American Society of Nephrology in 1992.[11]

MATERIALS AND METHODS
Methods

Urine and serum chemistries were evaluated in 6 pregnant women with pre-eclampsia on their first visit, immediately prior to delivery and postpartum. All of the patients were referred to the Division of Nephrology at the University of Connecticut Health Center for evaluation of proteinuria and hypertension. The FE_{urea} was calculated as follows:

$$FE_{urea} = [(\text{urine urea/plasma urea})/(\text{urine creatinine/plasma creatinine})] \times 100$$

Proteinuria was assessed by random urine protein-creatinine ratio or 24-hour urine protein studies. There is evidence of strong correlation between the two methods.[11]

Patients

Patient 1. A 26-year-old primigravida with a history of tuberous sclerosis, multicystic kidneys and CKD developed new onset hypertension in the last trimester (blood pressure, 150/98 mm Hg). The 24-hour urine protein excretion was 0.43 g at the 18th week of gestation. During the 27th week, proteinuria was 2.0 g and increased to 4.8 g on the day prior to caesarian section. Serum creatinine rose from 4.4 mg/dL at the 18th week to 5.8 mg/dL prior to delivery. Within 1 month after delivery, proteinuria decreased to 0.88 g/d and serum creatinine returned towards baseline (4.9 mg/dL).

Patient 2. A 24-year-old woman with a history of hypertension and proteinuria secondary to focal segmental glomerulosclerosis had 2 previous pregnancies which were terminated on medical advice due to her worsening CKD. During the 3rd pregnancy, blood pressure was as high as 190/120 mm Hg despite being on methyldopa. Four months before delivery, her serum creatinine was 2.5 mg/dL, and urine protein excretion was 5.6 g/d. During the last week of pregnancy serum creatinine rose to 2.8 mg/dL and proteinuria increased to 12 g/d. Her transaminases and lactate dehydrogenase also increased (aspartate aminotransferase, 474 U/L; alanin aminotransferase, 628 U/L; and lactate dehydrogenase, 1142 U/L), and platelet count decreased to 38×10^9/L. Within 1 month of delivery, serum creatinine and urine protein improved to 2.1 mg/dL and 7.5 g/d, respectively. Proteinuria further decreased to 4.2 g/d after 3 months.

Patient 3. A 31-year-old woman with type 1 diabetes mellitus presented with proteinuria started before pregnancy. Four months prior to delivery, proteinuria was 3.0 g/d. One month prior to delivery, blood pressure was 160/95 mm Hg, serum creatinine was 1.2 mg/dL, and proteinuria was 8.2 g/d. During the last week of pregnancy, hypertension worsened. Serum creatinine and proteinuria at the time were 1.9 mg/dL and 7.4 g/d, respectively. On the 2nd postpartum day, serum creatinine improved to 1.6 mg/dL and the blood pressure was 118/78 mm Hg.

Patient 4. A 26-year-old woman with a history of seizure but no kidney disease before pregnancy developed hypertension and proteinuria (6 g/d) in the last trimester and was diagnosed with systemic lupus erythematosus. Two weeks prior to the delivery, the patient was admitted for suspected grand mal seizure, visual disturbances, and nephrotic syndrome (urine protein, 10 g/d). She delivered twins after induction of labor. One month postpartum, proteinuria was still 6 g/d. A kidney biopsy revealed endotheliosis consistent with pre-eclampsia and no features of lupus nephritis. Proteinuria eventually improved to 1 g/d.

Patient 5. A 16-year-old primigravida with a history of systemic lupus erythematosus had worsening hypertension during the week prior to termination of pregnancy. Her serum creatinine rose from 0.8 mg/dL to 1.7 mg/dL, and proteinuria increased from 15 g/d to 22 g/d in the 21st week of gestation. Two days after termination of pregnancy, serum creatinine decreased to 1.2 mg/dL. Six weeks later, proteinuria decreased to 3.8 g/d.

Patient 6. A 33-year-old pregnant woman (36 weeks) develops new-onset hypertension and proteinuria. Her first pregnancy, 6 years earlier, had been complicated with pre-eclampsia. She had moderate lower extremity edema and her blood pressure was 140/75 mm Hg. A 24-hour urine collection revealed 774 mg of protein. Urine microscopy was insignificant. She was started on α-methyldopa. Her serum creatinine was 0.6 mg/dL and serum uric acid was 4.7 mg/dL. The patient delivered by induction of labor secondary to worsening hypertension and proteinuria at 36.5 weeks of pregnancy. Uric acid level was 4.3 mg/dL at the time of delivery.

RESULTS

The FE_{urea} was measured 7 to 3 days before, on the day of, and 1 days to 1 month after delivery or pregnancy termination. The Table and the Figure summarize the FE_{urea} measurements in the 6 pregnant women. In all of the patients with proteinuria and hypertension, a baseline FE_{urea} in the 3rd trimester was found to be 35% and higher

(47.5 ± 5.1%). Four patients had pregnancy CKD, proteinuria, or hypertension prior to conception. One patient was diagnosed with systematic lupus nephritis during the 3rd trimester, but a biopsy was inconsistent with lupus nephritis, and rather showed endotheliosis. All of the women were ultimately diagnosed with pre-eclampsia by clinical criteria (neurologic abnormalities, worsening hypertension, and/or proteinuria and elevated serum creatinine) with FE_{urea} values decreased to less than 35% (24.5 ± 3.9%; P = .01, when compared to baseline values). Eclapmsia, HELLP syndrome, and biopsy-proven endotheliosis were documented each in 1 patient. The 6th patient had features of pre-eclampsia without underlying kidney disease and is described here as an example of change in FE_{urea} in patients with pre-eclampsia only. In all of the patients, there was substantial improvement in proteinuria, serum creatinine or hypertension in the postpartum period. Within 3 days of delivery, the FE_{urea} returned to normal values (52.5 ± 3.7%, P = 0.01 when compared to pre-eclamptic values).

DISCUSSION

The pathophysiology of pre-eclampsia is complex. Several mechanisms have been suggested in the literature over the years. The recent discovery of circulating anitangiogenic factors, ie, circulating soluble fms-like tyrosine kinase 1 and soluble endoglin, is of great interest.[13] The focus of this discussion, however, is the justification of the decrease in FE_{urea} in pre-eclampsia as a consequence of proposed angiotensin II hypersensitivity in these patients.

In healthy women, plasma volume increases

Fractional Excretion of Urea Values During Pregnancy, Immediately Before Delivery, and Postpartum

Patient	Fractional Excretion of Urea, %		
	Prior to Delivery	At Delivery	After Delivery
1	66	28	45
2	42	33	46
3	45	34	59
4	37	24	68
5	35	8	47
6	60	21	50
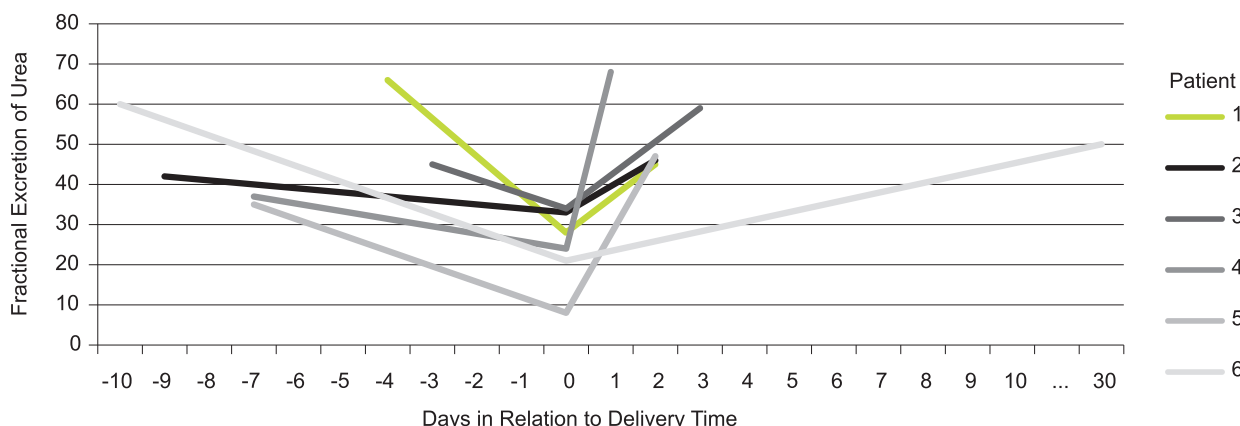
Fractional excretion of urea during pregnancy, immediately before delivery, and after delivery.

by 40% to 60% during pregnancy, and a relative endothelial refractoriness develops to the vasoconstrictor actions of angiotensin II.[3,5] The altered vascular response to angiotensin II is also evident by the findings reported by Baylis and Collins, as they observed no change in blood pressure by angiotensin II inhibitors in normal pregnant rats.[14] These physiologic adoptions assure ample vital organ perfusion including enhanced renal blood flow (RBF) and glomerular filtration rate. Davidson and colleagues reported effective RBF and glomerular filtration rate increments of more than 50% during pregnancy as compared to nonpregnant females. He also showed that the FE is reduced during pregnancy and only rises slightly (towards normal) at term.[15] Elegant micropuncture studies in pregnant rats have demonstrated equal afferent and efferent arteriolar dilatation, so that despite increased RBF there is no change in glomerular capillary hydrostatic pressure.[16] These observations provide plausible evidence of an angiotensin II insensitive state, given that, normally, angiotensin II causes relatively more efferent arteriolar constriction leading to increased glomerular capillary hydrostatic pressure and filtration fraction.[17,18] This effect of angiotensin II on efferent arteriole is supported by Hall and colleagues in nonpregnant dogs. They observed a decline in RBF of 85% with angiotensin II infusion and a filtration fraction decline of only 5% to 8%.[19]

The above changes are reversed in pre-eclampsia, paradoxically reducing systemic organ perfusion. Although, total plasma volume is contracted (30% to 40%) in pre-eclampsia, the "effective" circulatory volume appears to be increased as evident by suppressed renin and aldosterone and elevated B-type natriuretic peptide, relative to normal pregnancy.[20] The endothelial refractoriness to angiotensin II is lost.[13,21] The RBF and glomerular filtration rate decrease by up to 62% to 84%.[20,22] These changes remit dramatically postpartum. A well-recognized cause of hypertension in pre-eclampsia is increased peripheral vascular resistance due to an exaggerated response to angiotensin II and catecholamines.[23] There is a lack of evidence of increased circulating renin or angiotensin II in pre-eclampsia; rather their levels are relatively low.[13,24] Endothelial dysfunction due to angiotensin II receptor heterodimerization and presence of agonistic antibodies are suggested as possible

mechanisms of angiotensin II hypersensitivity.[1,13,24] These changes may precede the onset of overt hypertension by weeks to months.[20] Experimental evidence has shown that women destined to develop pre-eclampsia become progressively more sensitive to the pressor effects of infused angiotensin II after 18 weeks of gestation. In a group of 192 primigravid women studied by Gant and coworkers, normal refractoriness to the pressor effect of infused angiotensin II was seen in normotensive pregnant patients.[21,25] However, in those who developed pre-eclampsia, a loss of this response was seen prior to the onset of hypertension. A similar prospective study of angiotensin II pressor refractoriness was also conducted in pregnancies complicated by chronic hypertension.[26] In this study 63 pregnant patients developed superimposed pre-eclampsia. Both groups were resistant to effects of angiotensin II until 21st to 25th weeks of gestation; however, after 27 weeks, the group destined to develop pre-eclampsia showed a marked loss of refractoriness to angiotensin II. Several other studies have stressed the central role of angiotensin II in the pathophysiology of pre-eclampsia. Other observations include an increased activity of potent vasoconstrictors such as thromboxane A2 and endothelin-1 and suppression of the vasodilators such as prostaglandin 1 and nitric oxide.[1,13,20] Although the role of angiotensin II is well established in the pathogenesis of hypertension in pre-eclampsia, contrary to the above hemodynamic basis, decreased glomerular filtration rate has been attributed to certain morphological glomerular changes by some investigators.[13]

Urinary urea excretion is primarily dependent on RBF and is the result of glomerular filtration, but less tubular reabsorption. The increase in RBF during pregnancy results in increased urinary urea excretion. The FE_{urea} measures 50% to 65% in a normal individual. In normal pregnancy, however, this value is probably higher. A low FE_{urea} denotes enhanced tubular absorption. Two sites for net urea reabsorption have been identified; the proximal tubule and the inner medullary collecting duct. In high angiotensin II states such as hypovolumia or ineffective circulation or an angiotensin II hypersensitive state such as pre-eclampsia, efferent arteriolar resistance and filtration is increased. This allows for a near-normal glomerular filtration fraction when RBF is

decreased. The increased filtration fraction leads to a rise in protein concentration and oncotic pressure within the efferent arteriole, thus enhancing fluid reabsorption from the proximal tubule. Urea transport in the proximal tubule follows water reabsorption. Angiotensin II also promotes direct tubular transport of water, and in turn, urea.[10,22] Thus, the FE_{urea} is expected to be low in these patients. This relationship was further elucidated by our previous observations demonstrating an increased FE_{urea} and urine volume in a small group of patients with congestive heart failure after angiotensin-converting enzyme inhibition.[10]

Hyashi and colleagues evaluated changes in urinary excretion of multiple biochemical parameters in pre-eclampsia in comparison with normotensive pregnant and nonpregnant women.[22] They noted that although the ratio of urinary urea nitrogen to creatinine in normotensive pregnant women was 20% to 45 % higher than in nonpregnant patients; the ratio in pre-eclampsia was 20% below those with normotensive pregnancy.[22] This can be extrapolated to a decline in FE_{urea} in pre-eclampsia. Our observations are further complemented by the fact that the percentage decline in RBF in pre-eclampsia is in excess of the percentage increment during normal pregnancy, so that the resulting decline in RBF is far more than RBF in normal nonpregnant subjects.

Our interpretation of the FE_{urea} data is in agreement with the above pathophysiology and in vivo biochemical evidence. Of note, however, this study does not report data on the FE_{urea} in normal pregnancy. The observations of Hyashi and colleagues, as noted above, do seem to suggest that the FE_{urea} values in normal pregnancy are likely to be elevated, rather than depressed.

CONCLUSIONS

A decrease in FE_{urea}, to values associated with decreased renal perfusion ($\leq$ 35%), was observed as the clinical signs of pre-eclampsia were becoming more apparent. Soon after delivery, the FE_{urea} returned towards the normal range (50% to 65 %). We conclude that this observation needs further studies to confirm our findings that monitoring FE_{urea} may be of particular value in identifying the onset of pre-eclampsia in patients with kidney disease, proteinuria, and hypertension before pregnancy.

CONFLICT OF INTEREST

None declared.

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