SEMINARS IN
NEPHROLOGY

The Renal Response to Preeclampsia

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Proteinuria and decreased renal function are classic hallmarks of preeclampsia. The kidney, with its reliance on glomerular blood flow and glomerular barrier integrity, provides a unique window to view the preeclamptic disease process. This review briefly details the characteristic renal structural changes seen in preeclampsia and then focuses on the disordered renal hemodynamics and other determinants of ultrafiltration. Both renal blood flow and glomerular filtration rate (GFR) decrease in preeclampsia, although absolute values may remain above the nonpregnant range. A decrease in the ultrafiltration coefficient (K_f), in the order of 50%, either alone or in combination with reduced renal blood flow, is presented as the most likely mechanism for the decrease in GFR. Proteinuria develops, at least in part, secondary to impaired glomerular barrier integrity with a loss of size selectivity revealed by fractional dextran clearance studies and it is proposed, although yet to be proven, that this is accompanied by a loss of glomerular barrier charge selectivity.
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Preeclampsia, a pregnancy-specific disease, is a multisystem disorder whose renal manifestations include functional loss and proteinuria. The cause of preeclampsia remains obscure, and several of the leading theories are discussed in this issue and elsewhere.[1] Whatever the proximate cause, the results include widespread endothelial dysfunction, and in this respect renal function with its reliance on adequate glomerular blood flow and barrier integrity is particularly susceptible to these endothelial changes. Indeed, it is the kidney that has provided a unique window through which to view the disease process. In addition, the measurement of circulating markers of glomerular filtration rate (GFR) (ie, serum creatinine level), and, to some extent, the degree of proteinuria, aid in managing the disorder. This review focuses on the compromised glomerular hemodynamics and disordered glomerular barrier function in preeclampsia and discusses how these pathologic changes effect clinical markers such as GFR and protein excretion.

Structural Changes

The presence of endothelial cell swelling in glomeruli from women dying of eclampsia was noted as early as 1924,[2] and, more recently, histopathologic and morphometric examination of renal biopsy specimens and autopsy material has aided in the understanding of preeclampsia-induced end-organ pathology. However, an in-depth discussion of these morphologic changes is beyond the scope of this article. Those interested in detailed descriptions and images of the renal pathology, a précis of several disagreements in the literature that include variant immunofluorescent observations and whether or not preeclampsia is a cause of focal glomerular sclerosis, are directed to reports by Sheehan and Lynch[3] and Gaber et al.[4,5] A selective summary follows.

The kidneys of women dying after eclampsia appear pale and enlarged compared with those of gravidas dying from other causes, but with apparently normal renal function.[3] The glomeruli are enlarged and not hypercellular, caused by swelling of the intracapillary cells (primarily endothelial) that encroach on the capillary lumen, giving the appearance of a bloodless glomerulus. Changes vary with the severity of the lesion, but usually involve most of the capillaries in all glomeruli, and this swelling can be of sufficient magnitude to cause herniation of the tuft into the proximal tubule, a phenomenon termed *pouting*.[3,4] Although unusual, mesangial interposition and, even more rarely, crescents may be noted. The preeclamptic lesion, however, is most evident on ultrastructure examination, elegantly described in the pioneering work of Spargo et al,[6] and includes extensive swelling and vacuolization, primarily of the endothelial and less often of the mesangial cells, with few if any changes elsewhere. The

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Table 1 Renal Pathology in 176 Hypertensive Pregnant Women Diagnosed Clinically as Having Preeclampsia

Biopsy Examination Diagnosis	Number of Patients	Primigravidas	Multiparas
Preeclampsia	96	79	17
With nephrosclerosis	13	6	7
With renal disease	3	1	2
With both	2	1	1
Nephrosclerosis	19	3	16
With renal disease	4	2	2
Renal disease	31	12	19
Normal histology	8	0	8

Modified from Fisher et al.[10]

enlarged cells, containing increased quantities of vacuolated cytoplasm, impinge upon the capillary lumen and sometimes appear to obliterate it. The appearance of densities of amorphous extracellular debris, the presence of deposits, and/or fibrin tactoids, and the effect of regressive or reparative changes in postpartum biopsy specimens are discussed further in more extensive reviews.[3-5] Surprisingly, and of note, the foot processes are mostly intact despite considerable proteinuria. However, some cytoplasmic podocyte changes, likely secondary to the proteinuria, may be observed. The basement membrane is not thickened, but may appear so on light microscopy owing to fibrils produced by endothelial and mesangial cells.

Spargo et al,[6] who coined the phrase *glomerular endotheliosis*, initially claimed the lesion was pathognomic for preeclampsia. In contrast, others have described such lesions in nongravid women with a variety of glomerular lesions, nonpreeclamptic hypertensive pregnant women in abruption, and, more recently, in gravidas with uncomplicated pregnancy.[7,8] This latter claim deserves some comment.

Strevens et al[7,8] performed renal biopsy examinations on 36 hypertensive and 12 normotensive pregnant women (a discussion of the ethics of the study can be found in a letter exchange, BJOG 111:191-5, 2004). By noting glomerular endotheliosis in 5 of the normal pregnant volunteers, these investigators were questioning the previous literature in which the diagnosis of preeclampsia was established by the presence or absence of that lesion. However, their results revealed that under light microscopy the intensity of the lesion in normotensive gravidas, on a scale of 0 to 3, was 1+ in 4 of 5 specimens (often a subjective call between something and nothing for the pathologist), and 2+ in the other specimen. Similarly, electron microscopy showed a slight degree of endotheliosis in 5 specimens and mesangial cell interposition and electron dense deposits were not seen. Lesions in the preeclamptic specimens, however, were considerably more robust and, as would be expected, glomerular volume was increased significantly in those presenting with hypertension and proteinuria. Thus, these studies, in reality, confirm our experience that the lesion in its fully developed form is quite distinctive, and the term most investigators have used, *characteristic*, not *pathognomonic*, still is quite valid.

Renal biopsy examinations rarely have been performed in pregnancy for at least 2 decades now. This is because there are no indications for its use after gestational week 30, and it has no role in the management of hypertension that presents late in gestation. Furthermore, postpartum biopsy examinations offer very little prognostic value in counseling women about subsequent pregnancies.[5] In this respect, the more recent literature has focused on more atypical events, some biopsy examinations performed long after delivery, and one should be circumspect about their conclusions. Decades ago, however, biopsy examination in the immediate puerperium was performed more frequently because practitioners thought the result might help in planning future pregnancies. The conclusion of one large study involving 176 biopsy examinations still is valid today as to its effect on the clinical approach to the hypertensive gravida. In their study, Fisher et al[10] observed that the physicians' diagnoses of preeclampsia was "wrong" in 25% of primiparas and more often than not in multiparas, making any series suspect in which many of the women who were labeled preeclamptic were multiparous (Table 1). Also, and surprisingly, 18% of the primiparous subjects (29% of multiparas), had another parenchymal renal disorder, most of the glomerular variety. Glomerular endotheliosis usually reverses rapidly after delivery, the glomeruli resuming normal appearance within 2 to 3 weeks, but some investigators have attributed abnormalities present years after the putative disease to residua of the preeclamptic lesion.[4,5,9] Whether pure, as opposed to superimposed, preeclampsia leave permanent histologic residua, however, is disputed and discussed elsewhere.[4,5]

Table 2 Percent Change in GFR, ERPF, and Filtration Fraction, GFR Divided by ERPF in Preeclampsia Compared With Healthy Late Pregnant or Nonpregnant Controls

	GFR	ERPF	Filtration Fraction
Mean % change from late pregnancy controls (N = 23)	−32%	−24%	−9%
Mean % change from nonpregnant controls (N = 10)	−22%	−22%	−3%

NOTE. N = number of studies.
Modified from Conrad and Lindheimer.[12]

Table 3 Estimated Segmental Renal Vascular Resistances in Preeclampsia-Eclampsia

		Renal Vascular Resistance (dynes × sec × cm^5)			
		Afferent		Efferent	
Diagnosis	N	Total	Arteriolar	Arteriolar	Venular
Normal pregnancy	97	6,534*	2,524	1,877	2,090
Preeclampsia-eclampsia	65	15,994	11,296	1,779	2,976

NOTE. Segmental resistances estimated according to Gomez DM: J Clin Invest 30:1143–55, 1951.
N = number of subjects.
Modified from Conrad and Lindheimer.[12]
*Mean values from combining 5 publications.

Renal Hemodynamics

Both GFR and renal plasma flow (RPF) increase markedly in normal pregnancy. A significant increase often is evident during the luteal phase of the menstrual cycle,[11] continues to increase after conception, and peaks approximately 50% above nonpregnant levels in second trimester.[12] These increments are maintained through week 36, after which a decrease of 15% to 20% may occur. RPF increases 50% to 80% during the initial trimesters, decreasing approximately 25% thereafter, but still remaining substantially above nonpregnant levels. Why these increments occur, including how the physiologic dilation of pregnancy effects the renal vasculature, gestational changes in glomerular-tubular feedback and renal autoregulation, increases in circulating relaxin and endothelin levels, or the production of endothelial relaxing factor(s), are discussed elsewhere.[12-14] Of importance, the stimuli for increased GFR and RPF appear to be maternal in origin, and micropuncture studies in pregnant rats involves similar decreases in the tone of the pre- and postglomerular arterioles so that intraglomerular pressure does not increase.[12-14]

Both renal blood, effective renal blood flow (that component of renal blood flow subject to ultrafiltration), and GFR decrease in preeclampsia, although absolute values may remain within the normal nonpregnant range. In a review by Conrad and Lindheimer,[12] renal hemodynamic data from 23 studies of preeclamptic women were compared in terms of GFR and effective RPF (ERPF) (mainly measured by renal clearances of inulin and para-aminohippurate, respectively). The results are summarized in Tables 2 and 3. All 23 studies were characterized by a decrease in GFR, and all but one had a decrease in ERPF in preeclampsia compared with matched late pregnancy controls. Nine of the 10 studies had postpartum data that revealed that the preeclamptic GFR and ERPF values were lower than nonpregnant levels.

The critical determinants of GFR are ERPF, the ultrafiltration coefficient K_f (the product of the available surface area for ultrafiltration and the porosity of that surface), and the Starling forces acting across the glomerular barrier (the net oncotic pressure and the transglomerular hydrostatic pressure difference [ΔP]). Because ΔP is not thought to change, at least in normal pregnancy,[15,16] and hypoalbuminemia would decrease intraglomerular oncotic pressure favoring ultrafiltration, a decrease in K_f and a decrease in ERPF, either separately or in combination, are the potential mechanisms for the net decrease in GFR (see later).

High renal vascular resistance caused primarily by increased afferent arteriole sphincter tone probably is responsible for the decrease in ERPF consistently seen in preeclampsia.[12] In this respect, Conrad and Lindheimer[12] estimated total renal vascular, afferent arterial, efferent arterial, and venular resistances, respectively, in 97 normotensive and 65 preeclamptic or eclamptic women from 5 studies. The almost 3-fold increase in total resistance was caused by a more than 4-fold increase in afferent resistance, a small increment in venular resistance, but little change in efferent resistance, respectively (Tables 2 and 3). This may serve a protective role in preeclampsia, autoregulating intraglomerular pressure, maintaining it within narrow limits despite systemic hypertension.

Renal Handling of Protein in Pregnancy

Qualitative and quantitative assessment of protein excretion are used routinely in the detection and monitoring of renal disease. The urinary proteins are both glomerular and tubular in origin, and not all are detected by the standard methods used in clinical laboratories. The situation becomes more complex because during gestation certain pregnancy-specific proteins appear in the urine. Thus, when assessing protein excretion in pregnant women it is imperative to establish normal values (including for one's own hospital laboratory), and not to rely on standards determined from nonpregnant populations. In this respect, it appears that in nonpregnant individuals, urinary total protein excretion (TPE) averages 20 to 80 mg/24 hour, with an upper limit of 150 mg/24 hour, with urinary albumin excretion (UAE) contributing 40% of this total. During pregnancy both TPE and UAE have been reported to be increased significantly, at least after the 20th gestational week. For example, 2 well-performed cross-sectional studies[17,18] and a small longitudinal study (the latter from preconception through pregnancy and for several months postdelivery[19]), suggest the following means (and upper limits) for 240 hour TPE and UAE, 200 mg/24 hour (300 mg/24 hour), and 12 mg/24 hour (20 mg/24 hour), respectively.

The increased urinary protein excretion in normal pregnancy, although significant, is minimal despite the marked gestational increases in renal hemodynamics. In fact, not all find urinary albumin increased in pregnancy (however, few investigators detail whether they have validated their immunoassays for pregnancy samples). There have been sporadic studies of urinary excretion of both small molecular weight circulating as well as tubular-produced proteins.[12] Of interest is a study by Bernard et al,[20] who attempted to identify specific glomerular and/or tubular alterations in pregnancy by measuring the urinary excretion of 4 low molecular weight proteins whose plasma concentrations were unaltered by pregnancy. Retinol binding protein, Clara cell protein, β_2-microglobulin, and α_1-microglobulin each are considered to be almost freely filterable, but their urinary excretion is minimal owing to almost complete tubular reabsorption. Comparing their excretion rate with that of the negatively charged albumin (whose excretion reflects, in part, the size and charge permselective properties of the glomerular barrier), they concluded that a physiologic decrease in the reabsorption capacity of the proximal tubule was, at least in part, responsible for the gestational increase in TPE.

Proteinuria in Preeclampsia

Increased proteinuria is a hallmark of the preeclamptic syndrome, de novo hypertension plus an increase in excretion to 300 mg/24 hour or greater, occurring after midpregnancy, being the research definition for diagnosing the disease suggested by both the International Society for the Study of Hypertension in Pregnancy, and the National High Blood Pressure Education Program. However, the degree of proteinuria, which may range from minimal to the nephrotic range, is not an important predictor of maternal or fetal outcome,[21] and, in fact, other clinical evidence of the preeclampsia syndrome (and occasionally histologic renal changes[10]) has been observed in approximately 10% of women presenting with de novo hypertension, but without proteinuria during late gestation. Thus, when de novo hypertension presents late in pregnancy, astute physicians treat such patients similar to those with the classic or research definition of the disease.

Because in preeclampsia the increases in renal hemodynamics are blunted or absent, and the abnormal proteinuria is mainly albumin, the increments must result from alterations in glomerular permeability and/or altered tubular handling of filtered proteins. Studies relating to microalbuminuria in pregnancy are limited, but such abnormalities may predict preeclampsia in diabetic patients (see article, "Strategies to Prevent and Treat Preeclampsia: Evidence From Randomized Controlled Trials", by Villar et al in this issue), but otherwise there does not appear to be a prewarning phase of increasing albumin excretion.[22] Of interest, are reports of increased UAE (>14 mg/24 hour) 3 to 5 years after preeclampsia, which may reflect residual glomerular damage from gestational protein trafficking[23] and/or covert renal anomalies.[24]

Glomerular Barrier Function

Size Selectivity

Once tubular protein reabsorption is saturated (TPE > 1 g/24 hour), the renal clearance of plasma proteins can be compared directly with their molecular weight, enabling evaluation of the size selectivity of the glomerular barrier. In selective proteinuria, the glomerular barrier hinders larger molecules, however, this capacity is lost in nonselective proteinuria. Although not a universal observation, the proteinuria of preeclampsia is considered to be nonselective,[12] but this literature is limited, and comprehensive glomerular barrier interrogation studies still are needed.

Barrier function in normal pregnancy has been assessed by our group[15,16] by using infusion of neutral dextran-40, which, similar to inulin, is neither secreted nor reabsorbed by the renal tubule, resulting in a urinary clearance equal to its glomerular filtration.[25] Results suggest that the normal gestational hyperfiltration is caused by increments in ERPF without a change in intraglomerular pressure (ΔP), K_f increases, and that a significant nondiscriminating shunt (derived by mathematic modeling of fractional clearance data) appears concomitantly with increasing proteinuria. All changes resolve sequentially (the shunt component being the last) by 4 to 5 months after delivery.

We are aware that the inability to measure ΔP in humans precludes precise estimation of K_f. However our studies[27] show a substantial decrease in K_f in preeclamptic women (50%) studied prepartum, compared to their own postpartum values as well as to data from normotensive third trimester controls. The magnitude of this change leaves little doubt that the attenuated K_f compromises preeclamptic glomerular ultrafiltration in association with decreased ERPF. A study performed by Lafayette et al[28] during postpartum period, post caesarean section, though methodologically problematic, also endorsed a decrease in K_f (see later). This has been shown to be the case in nephrotic nonpregnant humans,[29] in whom reductions in K_f were in proportion to structural changes ascribed to a reduced glomerular permeability to water (termed, *k*).

It appears paradoxic that structural changes that hinder the ultrafiltration of water and might reasonably be expected to retard the passage of proteins, do not. One possible explanation is that broadened podocyte foot processes capable of reducing k may, in a small proportion, completely disrupt the integrity of the slit diaphragm. This then would allow for high loss of protein in small pockets of the glomerular wall while only contributing to a small increase in the net flux of water. Such an effect was supported by the theoretical models termed *log-normal* and *isoporous plus shunt* that we used to analyze neutral dextran sieving data in preeclampsia.[27] In the log-normal model the variation in pore size around the mean was increased (S), whereas the shunt component (ω_0) that accounts for the free passage of large molecules of the isoporous model also was increased. Each model therefore supported a loss of size selectivity in preeclampsia (Table 4). A second explanation for the enhanced transglomerular loss of

Table 4 Theoretical Glomerular Permselective Properties in Normal Late Pregnancy and Preeclampsia Applying the Lognormal Model and Isoporous Plus Shunt Models to Serial Neutral Dextran Sieving Data

Study Groups	Ultrafiltration Coefficient mL/min/mm Hg	Isoporous Diameter (nm) + Shunt Component (ω_0)	Lognormal Mean Pore Size (nm) +/− Variation Around the Mean (S)
LP controls, n = 14	8.94	6.27 + 0.0063	5.63 ± 0.115
LP preeclampsia, n = 10	4.64	6.17 + 0.0071	5.28 ± 0.118
PP controls, n = 14	7.93	6.29 + 0.0030	5.84 ± 0.112
PP preeclampsia, n = 5	8.06	6.09 + 0.0042	5.49 ± 0.114

NOTE. In each, a transglomerular pressure (ΔP) of 40 mm Hg was assumed.
Abbreviations: LP, late pregnancy; PP, >5 months postpartum.
Data from Moran et al.[27]

protein despite a decrease in k is a loss of glomerular wall charge selectivity as discussed later.

Glomerular Wall Charge Selectivity

The transglomerular filtration of the negatively charged albumin is restricted to a much greater extent than would be expected from its size alone. In nonpregnant studies, Chang et al[25] examined the effect of molecular charge by comparing the filtration of neutral dextran with the structurally similar, but anionic polymer, dextran sulfate. There was a greater measurable restriction to the passage of dextran sulfate for all effective dextran radii larger than 2.1 nm, and at radii smaller than this both dextran and dextran sulfate were filtered freely. Bohrer et al[30] found the converse to be true for the highly cationic form of dextran-diethylaminoethyl dextran, the fractional clearance of which was enhanced over the entire range of radii studied (1.8-4.2 nm) compared with neutral dextran (see Table 5). These different fractional clearance rates can be explained by the negative, fixed charge found on all layers of the glomerular barrier. Because the majority of proteins are anionic, for a given epithelial pore size or podocyte slit space an anionic macromolecule will be repelled and see a smaller space than a neutral molecule.

Loss of the glomerular barrier charge is implicated in the development of several nephropathies usually coupled with a size-selective defect. Unfortunately, charged dextrans are not suitable for use in human pregnancy and alternative techniques are required.

Indirect evidence from renal biopsy studies have raised the possibility that preeclamptic morphometric changes might lead to or result from a loss of charge selectivity.[31] In specimens obtained 2 weeks postpartum from 15 African women with early onset preeclampsia the glomeruli were enlarged in 50%, with fusion of podocyte foot processes (80%) and the glomerular basement membrane was thickened in two thirds of these women. These ultrastructural changes were seen in combination with a significant decrease in the amount of anionic heparin sulfate in the glomerular basement membrane. The loss of negative charge on the podocyte surface was implied because the repelling action of adjacent cell membranes is thought to be necessary to maintain the numerous narrow slits characteristic of the podocyte epithelial cell layer. However, we stress that these biopsy examinations were performed 2 weeks postpartum and may represent an atypical patient population. Postpartum preeclamptic renal biopsy examinations also have been assessed by Lafayette et al[28] in an attempt to derive filtration parameters for the glomerular barrier, using morphometric analysis and theoretical modeling of 13 women at 48 hours after caesarean section. The validity of this has been questioned for the following reasons: the heterogeneous postpartum population; failing to control for differences in glomerular hemodynamics; use of pharmacologic manipulations; and contrary to most other studies in the literature (Table 3), ERPF in their preeclamptic patients was similar to the normotensive postpartum controls, thus making this one of the rare studies that failed to show some hemodynamic contribution to hypofiltration in preeclampsia.[28] Still, the investigators modeling results suggested a decrease in K_f of approximately 40%. Subendothelial deposits, endothelial and mesangial cell hypertrophy, and swollen endothelial segments without fenestrae reduced the effective filtration surface area by a third. This was offset by the increased overall glomerular volume, resulting in a net reduction of only 10%. Morphometric analysis led to the conclusion that hypofiltration was caused by a decrease in K_f secondary to decreases in both porosity and available filtration surface area.

Table 5 The Effect of Charge on the Clearance of Macromolecules at a Molecular Radius of 3.6 nm

Macromolecule	Fractional clearance ($\theta_{macromolecule}/\theta_{inulin}$)
Albumin (anionic)	0.003
Neutral dextran	0.15 ± 0.02 (n = 15)
Dextran sulphate (anionic)	0.01 ± 0.002 (n = 15)
Dextran-diethylaminoethyl dextran (cationic)	0.42 ± 0.06 (n = 9)

NOTE. θ = urinary/plasma concentration. A freely filtered molecule will have a fractional clearance of 1.
Modified from Brenner et al,[47] and Galaske et al.[43]

Renal Handling of Uric Acid

Serum uric acid levels are 25% to 35% lower in normal pregnancy, increasing toward nonpregnant levels in the third trimester.[12,32] This is caused by increases in the fractional clearances of urate, their being little evidence of changes in its

production rate or other aspects of its metabolic clearance.[12] Uric acid measurements have long been central to diagnosis and management of preeclampsia because hyperuricemia, caused in part by decrements in fractional urate clearance, may precede significant proteinuria and correlates with renal histologic disease severity,[33] blood pressure, perinatal mortality,[34] and perinatal morbidity.[35]

By using probenecid to inhibit the tubular reabsorption of uric acid, Czaczkes et al[36] observed but a modest decrease in serum values in 3 normal pregnant women. In 15 preeclamptic patients, however, probenecid significantly augmented renal clearance and restored circulating uric acid to values normal for pregnancy (but had little effect on the course of the disease). These data imply that hyperuricemia in preeclampsia is caused primarily by enhanced tubular reabsorption. The underlying mechanism is unknown but because sodium and uric acid reabsorption are coupled, hyperuricemia may be a by-product of enhanced sodium reabsorption, akin to what occurs when intravascular volume is decreased. Hyperuricemia in preeclampsia may be of benefit, protecting against increments in oxidative stress that may accompany the disorder. Such increments, said to result from an imbalance between prooxidant and antioxidant forces in the disorder, are discussed elsewhere in this issue (see article by Roberts and Speer in this issue) favor the formation of oxygen free radicals, which can lead to the formation of lipid peroxides and cellular damage. Lipid peroxide levels increased in normal pregnancy are increased further in preeclampsia, correlating with increasing blood pressure, although not perinatal outcome.[37] The ability of plasma to neutralize free radicals is augmented in preeclampsia, primarily owing to the antioxidant action of uric acid.[38] Increased tubular uric acid reabsorption may, therefore, represent an appropriate response to systemic oxidative disequilibrium, rather than an indication of reduced filtered load or compromised renal tubular function.

Volume and Sodium Homeostasis

Normal healthy pregnancy is characterized by a decrease in systemic vascular resistance and mean arterial pressure with a concomitant increase in cardiac output[39] (see article, "Cardiovascular Changes in Preeclampsia", by Hibbard et al in this issue). To accommodate these changes, plasma volume expansion must occur. This is achieved by a subtle shift in sodium balance with a 3- to 4-mmol/24-hour increase in sodium retention leading to an overall gain of approximately 900 mmol over a period of 9 months. Indeed, the daily tubular recovery of the marked increase in filtered sodium ($[Na]_{plasma} \times GFR$) of many thousands of mmol per 24 hours is the greatest challenge presented to the kidney during normal gestation.

The capacity to excrete sodium is compromised in preeclampsia, suggesting either a primary renal defect or that the decreased plasma volume is sensed as a true decrease and sodium is retained as an appropriate renal response.[40] The complexities of sodium handling may be shown by the reciprocal actions of atrial natriuretic peptide (ANP) and the renal-angiotensin-aldosterone system (RAAS). ANP is not only natriuretic and diuretic, it is also a vasodilator and RAAS antagonist. Circulating ANP levels are increased in pregnancy and, paradoxically, further increased in preeclampsia. This may be explained by the decreased metabolic clearance of ANP in preeclampsia,[41] making it likely that the heart senses the reduced intravascular volume as such, while continuing to secrete ANP in proportion to atrial stretch.

All components of the RAAS are lower in patients with preeclampsia compared with normal pregnant controls, but usually are higher than in the nonpregnant state.[42] The normal pregnancy refractoriness to angiotensin II is, however, lost and antedates clinical signs.[44] Reasons for these alterations are obscure and one article in this issue ("AT1 Receptor Agonistic Antibodies, Hypertension, and Preeclampsia" by Dechend et al) discusses the presence of autoantibodies to angiotensin II agonistic to the AT I receptor. We focused on ANP because it antagonizes the RAAS at many levels. It decreases plasma renin activity, suppresses basal and stimulated aldosterone (ALDO) production and ALDO-mediated renal sodium reabsorption, and inhibits all the known actions of angiotensin II. These mechanisms have been shown to be intact in normal and preeclamptic pregnancy.

ANP infusion in normal pregnancy (designed to increase plasma concentrations while remaining within physiologic limits) decreases plasma renin activity and ALDO concentrations, evoking a prompt natriuresis.[45] In preeclamptic primigravidas, baseline ANP levels were increased and ANP infusion produced a similar decrease in ALDO although the already low plasma renin activity was not suppressed further. A role for ANP as an antagonist of the RAAS in preeclampsia therefore is emerging, and it is possible that these antihypertensive actions are at least as important as its role in volume homeostasis.

Subtle changes in renal sodium handling are difficult to measure with standard techniques. Compared with normal pregnant controls, however, in preeclampsia there is a 5-fold decrease in the ALDO/ANP ratio favoring sodium excretion despite similar net sodium excretion rates.[45] This, interestingly, may be caused by deficient aldosterone synthase activity in those who develop the disease.[46] In preeclampsia the reduced ability to excrete a sodium load is, therefore, likely to result from a reduced sodium load despite altered tubular handling favoring sodium loss. More comprehensive accounts of this controversial area have been published.[40,47]

Acute Renal Failure in Preeclampsia

Despite oliguria or anuria and the marked structural and functional changes described earlier, acute renal failure (ARF) is unusual in patients with severe preeclampsia.[4,13] If ARF is uncomplicated by preexisting renal disease, the vast majority of patients regain normal function, but full recovery

may not occur when there is underlying renal pathology, often undetected and unsuspected before pregnancy.

ARF complicating pregnancy usually is caused by acute tubular necrosis that is severe enough to require dialysis and has an incidence of 1:10,000 to 20,000. Pregnant populations once were considered more susceptible to renal cortical necrosis than nonpregnant populations, but that complication, too, now is extremely rare (1:80,000).[13] Those preeclamptic patients also facing hemorrhagic complications are particularly at risk because further decreases of an already contracted intravascular volume, vasoconstriction plus enhanced vascular reactivity, and glomerular endothelial swelling producing capillary obstruction lead to postglomerular ischemia and acute tubular necrosis. The treatment of ARF is similar to that for nonpregnant women. The caregiver, however, must take into account the changes in the levels of solutes such as sodium, bicarbonate, and creatinine, as well as the physiologic volume changes of normal gestation, regarding therapeutic interventions. Dialytic therapy, for instance, often is started earlier and performed more frequently in such cases.

Conclusions

Preeclampsia is a multisystem disorder of unknown cause and without a totally unifying hypothesis. The endothelium is targeted at an early stage resulting in disordered renal vascular sensitivity and glomerular dysfunction. Whereas systemic vascular endothelial cell dysfunction leads to changes that are not measured easily in clinical practice, glomerular endothelial involvement results in hypofiltration and a loss of permselectivity with measurable changes in the amount and composition of the urine produced. The kidney, therefore, provides a unique opportunity to study the pathogenesis of preeclampsia, remains central to its diagnosis and management, and may allow assessment of subtle and remote effects of the disorder as well.

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