

NEPHROLOGY

Rounds™

Pregnancy and the Kidney

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Approximately 5% of pregnancies are affected by preeclampsia, making it one of the most common complications of pregnancy. This issue of *Nephrology Rounds* discusses the functions of the kidney in normal pregnancy and presents an overview of the causes, symptoms, diagnosis, complications, and management of preeclampsia. This issue also presents a brief discussion of peripartum hypertension without proteinuria and how pre-existing renal disease and lupus erythematosus may affect pregnancy.

Normal pregnancy

A normal pregnancy is associated with an increase in cardiac output and a reduction in systemic vascular resistance. The usual marked increase in uterine blood flow does not entirely account for these changes; vascular resistance to regional blood flow is also lowered in extrauterine tissues. Systemic blood pressure (BP) during normal pregnancy is usually lower than it is either before or after the pregnancy. All these changes tend to regress during the last trimester as delivery approaches.¹ Renal blood flow and glomerular filtration rate (GFR) increase by about 35%-50% during normal pregnancy. The clearance of creatinine rises immediately after the first missed menstrual period, becoming significantly elevated by the fourth gestational week. Starting about 4 weeks from term, renal hyperemia diminishes.²

As the GFR increases during pregnancy, serum creatinine and blood urea nitrogen fall. Urate clearance increases and serum uric acid falls.³ Renal glycosuria is not uncommon. The urinary excretion of protein also rises, so that slight microalbuminuria may occur. Women with chronic inactive glomerulonephritis, in whom pre-pregnant levels of protein excretion are <1 gram daily, may excrete 2 to 6 grams of protein in the urine during a normal pregnancy because of glomerular hyperemia, without any other sign of exacerbation of the nephritis. In such women, plasma uric acid levels generally do not rise if preeclampsia is not present.

The size of the kidneys increases in gestation, renal lengths increasing by about 1 centimeter when measured radiographically or by ultrasound.³ The collecting systems of both kidneys are normally dilated during pregnancy and is most marked on the right. An unusual syndrome may occur during late pregnancy that is characterized by abdominal pain, marked hydronephrosis, and a variable increase in serum creatinine. It is managed successfully by the placement of ureteral stents.⁵ Because "physiological hydronephrosis" is so common, pregnant women are particularly susceptible to ascending pyelonephritis as a result of bladder infections.

Serum sodium is commonly reduced during normal pregnancy by 4 to 5 mEq/L below non-pregnant levels, with a decrease in the level of osmotic pressure necessary to induce thirst and secretion of antidiuretic hormone. The changes in osmotic threshold can be reproduced in nonpregnant women by the injection of human chorionic gonadotropic hormone.⁶ Pregnancy increases the expression of the aquaporin 2 water channel in the renal papilla of rats,⁷ perhaps contributing to water retention. Normal pregnancy is also characterized by compensated respiratory alkalosis, with a reduction in arterial pCO₂ and serum bicarbonate.⁸ As a result, the serum bicarbonate of normal pregnant women may be as low as 18 mEq/L. Slightly low serum bicarbonate in a pregnant woman, therefore, should not be misinterpreted as indicating metabolic acidosis. After overbreathing is compensated by renal excretion of bicarbonate, as is usual during pregnancy, urinary pH becomes normally acid.

Circulating levels of 1,25 hydroxy vitamin D₃ are increased during normal pregnancy and the intestinal absorption of dietary calcium increases.⁹ Urinary excretion of calcium is also increased, leading to a tendency in some women to form kidney stones. Circulating levels of vasopressinase, an enzyme that hydrolyzes arginine vasopressin, are increased

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during normal pregnancy. Occasionally, this increase is so pronounced that circulating antidiuretic hormone (arginine vasopressin) disappears, resulting in the polyuria and polydipsia of diabetes insipidus. The symptoms usually remit after delivery, when vasopressinase levels fall to normal. The diabetes can be controlled by the administration of dDAVP, which is not destroyed by vasopressinase.¹⁰

Pregnancy has long been known to confer a peculiar susceptibility to the vascular effects of gram-negative endotoxin (Shwartzman phenomenon). Perhaps because of the physiological increase in pro-coagulant factors that occurs in normal pregnancy, the thrombotic microangiopathy and renal cortical necrosis that characterize septic shock are particularly pronounced during pregnancy. Renal cortical necrosis is a common complication, for example, of septic abortion.¹¹

Preeclampsia

Preeclampsia, the most frequently encountered renal complication of pregnancy, is characterized by new hypertension and proteinuria, usually detected during the last trimester of pregnancy. It is commonly associated with edema and hyperuricemia. Preeclampsia usually remits when the placenta is delivered. The placenta in preeclampsia is often abnormal, with evidence of hypoperfusion and ischemia. Vascular endothelial dysfunction and microangiopathy are present in the mother, but not in the fetus. The predominant target organ may be the brain (seizures or eclampsia), the liver (hemolysis elevated liver enzymes low platelets count [HELLP] syndrome), or the kidney (glomerular endotheliosis and proteinuria). Preeclampsia probably has its origins in disordered development of the placenta which, in turn, leads to widespread maternal endothelial effects. Preeclampsia complicates approximately 5% of all pregnancies, making it perhaps the most common glomerular disease of the kidneys in the world.

Preeclampsia is about twice as common in first pregnancies as in later ones. Other predisposing factors include preexisting hypertension, chronic renal disease, obesity, diabetes mellitus, thrombophilias, and multiple gestations.¹² It occurs more frequently in women whose mothers had preeclampsia and in women whose fathers were products of a preeclamptic pregnancy.¹³

Hypertension

Increased peripheral vascular resistance, rather than increased cardiac output, is the chief cause of hypertension.¹⁴ As in other forms of hypertension, sympathetic activation is prominent^{15,16} and there is an exaggerated response to infusions of angiotensin II and other hypertensive stimuli.^{17,18} A feature that distinguishes the hypertension of preeclampsia is suppression, rather than activation, of the renin-angiotensin-aldosterone system.¹⁹ This suggests that vasoconstriction, increased peripheral vascular resistance, and renal salt and water retention are initial events, resulting in an increased perceived effective circulating blood volume with subsequent suppression of renin and aldosterone. Although total plasma volume is

slightly decreased, the hypertension of preeclampsia is exacerbated by salt loading and at least partly ameliorated by diuretics and salt deprivation.²⁰ A comparable decrease in total plasma volume with an increase in peripheral vascular resistance and arterial BP can be produced by the infusion into normal subjects of norepinephrine and other vasoconstrictors.²¹ The vasoconstriction of preeclampsia appears to be mediated by alterations in several vasoactive molecules, including the vasoconstrictors, norepinephrine, endothelin, and perhaps thromboxane, and the vasodilators prostacycline and perhaps nitric oxide.²²⁻²⁴ These vasoactive substances, which appear to mediate the hypertension of preeclampsia, are largely synthesized by the vascular endothelium, supporting the hypothesis that endothelial dysfunction may underlie the hypertension of preeclampsia.

Edema

Sudden weight gain, with edema of the feet, hands, and face, is a common presenting symptom in preeclampsia. Patients with preeclampsia excrete a much smaller percentage of an intravenous saline load than do normal pregnant women.²⁵ Suppression of renin and aldosterone levels suggests primary renal retention of salt and water. The edema of preeclampsia thus resembles the “over-fill” edema of acute glomerulonephritis or of acute ischemic renal failure with volume overload.²⁶ Other contributing factors to the edema may be a generalized increase in capillary permeability and hypoalbuminemia.

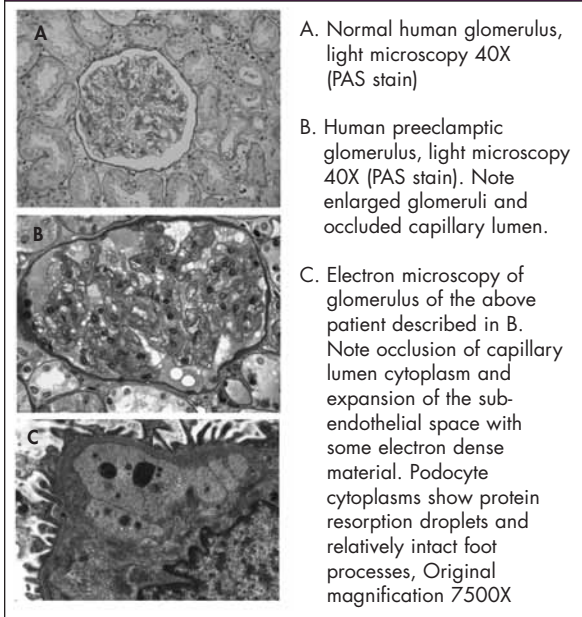
Renal function, proteinuria, and the urinary sediment

While in normal pregnancy, GFR and renal plasma flow increase during early and mid-pregnancy; in preeclampsia, GFR and renal plasma flow are uniformly decreased. Blood urea nitrogen (BUN) and serum creatinine often remain in the normal non-pregnant range, despite a significant decrease in GFR from the elevated levels of normal pregnancy. The proteinuria of preeclampsia is “non-selective.”²⁷ The filtration fraction (GFR divided by renal plasma flow) is lower during preeclampsia than in normal women during the last trimester of pregnancy.^{27,28} The urinary sediment is usually “bland” in preeclampsia, with few or no white blood cells, red blood cells, or cellular casts. After delivery, proteinuria usually disappears within 7-10 days although, in a few women, it may persist, though gradually diminishing, for 3-6 months.

Uric acid

A disproportionate fall in uric acid clearance is a key feature of preeclampsia. The serum level of uric acid rises as preeclampsia progresses; a level >5.5 mg/dL is a strong indicator of the disease and a level >7.8 mg/dL is associated with significant maternal morbidity. The degree of uric acid elevation correlates with the severity of proteinuria and renal pathological changes, and with fetal demise.²⁹ Efforts to lower blood uric acid by the administration of probenecid for up to 7 days do not appear to alter the

Figure 1: Glomerular endotheliosis



hypertension and proteinuria of preeclampsia.³⁰ The hyperuricemia is analogous to the disproportionate fall in urate clearance produced in normal human subjects by vasoconstrictors like norepinephrine.³¹ Recent rodent studies suggest that hyperuricemia may also play a pathogenic role by contributing to the vascular damage and hypertension.³²

Renal pathology

Preeclampsia is associated with a unique and specific appearance of the glomeruli of the kidney, referred to as “glomerular endotheliosis”³³ (Figure 1). By light microscopy, the glomerular capillary lumen is narrowed and appears bloodless, and the glomeruli are enlarged. Unlike other thrombotic microangiopathies, the endotheliosis of preeclampsia is usually not accompanied by prominent capillary thrombi. Immunofluorescence may reveal fibrin deposits, especially when systemic thrombotic microangiopathy is prominent. Unlike other examples of the nephrotic syndrome, the electron microscope shows relative preservation of the podocyte foot processes.³⁴ Loss of endothelial fenestrae is also seen by electron microscopy. Mild glomerular endotheliosis has been noted in up to 30% of patients with pregnancy-induced hypertension without proteinuria,^{35,36} suggesting that some cases of pregnancy-induced hypertension may reflect an earlier or milder form of preeclampsia. The glomerular changes usually disappear within 8 weeks of delivery, coinciding with resolution of the hypertension and proteinuria. Focal glomerular sclerosis is said to accompany the generalized glomerular endotheliosis of preeclampsia in up to 50% of cases.³⁵

Neurological and coagulation abnormalities

The sudden appearance of seizures (eclampsia), together with headache, blurred vision, or temporary loss of vision, has been attributed to brain edema, microvascular-

thrombi, and cerebral vasoconstriction. Hyperactive tendon reflexes often precede convulsions. Sudden, marked elevation of BP usually contributes to the severe cerebral edema that is a hallmark at post mortem examination of patients who die of eclampsia. Treatment with intravenous magnesium sulfate usually lowers BP and reduces central nervous system irritability, but does not improve renal function.

The tendency of blood to coagulate is increased during normal pregnancy because of an increase in circulating levels of all coagulation factors, including those made in the liver and in the vascular endothelium.³⁷ In the indolent microangiopathy of preeclampsia, however, it is only those factors synthesized in the vascular endothelium that are elevated.³⁸ Preeclampsia is sometimes complicated by severe thrombotic microangiopathy and consumptive coagulopathy that culminates in the HELLP syndrome.

Abnormal placentation in preeclampsia

The characteristic placental lesion in preeclampsia is a diminution in endovascular invasion by cytotrophoblasts and a decrease in remodeling of the uterine spiral arterioles.³⁹ The hypothesis that defective trophoblastic invasion with accompanying utero-placental hypoperfusion may lead to preeclampsia is supported by animal and human studies. Pathologic examination of placentas from pregnancies with advanced preeclampsia often reveals numerous placental infarcts and sclerotic narrowing of arterioles.⁴⁰ In one-third to one-half of preeclamptic women, however, these changes are not pronounced. Ultrasound estimation of utero-placental blood flow is usually diminished in preeclamptic women.⁴¹ Placental ischemia, induced by mechanical constriction of the uterine arteries or aorta, produces hypertension, proteinuria and, variably, glomerular endotheliosis, in several animal species.⁴² However, placental ischemia alone, as seen in many cases of intrauterine growth restriction, does not appear to be sufficient to produce preeclampsia. Thus, although utero-placental ischemia is an important trigger of preeclampsia, it may be absent in some cases and the maternal response to placental ischemia is variable.

The preeclampsia factor and anti-angiogenic state

The search for a circulating factor that causes the maternal syndrome of preeclampsia has been an area of intense investigation. Suggested factors include neurokinin-B, hypertensive heterodimers of angiotensin receptors, agonistic antibodies to angiotensin receptors, oxygen-free radicals, and exportation of diseased trophoblastic fragments.⁴³⁻⁴⁶

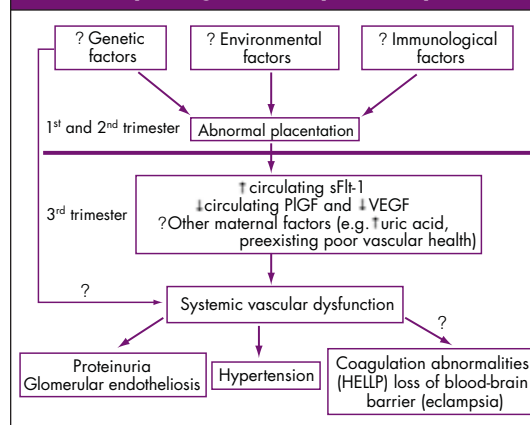
Recently, gene expression profiling has been used to search for candidate factors produced by the placenta in preeclampsia. Using this approach, the mRNA for sFlt-1 (soluble FMS-like tyrosine kinase-1) was found to be upregulated in preeclamptic placentas.⁴⁷ sFlt-1 is a secreted protein, a splice variant of the VEGF (vascular endothelial growth factor) receptor Flt-1, which lacks the transmembrane and cytoplasmic domain of the membrane-bound

receptor. Circulating in the blood, it acts as a potent antagonist to VEGF and placental growth factor (PlGF). Both VEGF and PlGF are made by the placenta and circulate in high concentrations during pregnancy. VEGF is also synthesized by the glomerular podocytes, as well as by vascular endothelial cells. Circulating sFlt-1 levels are greatly increased in women with established preeclampsia and prior to onset of clinical symptoms.⁴⁸ Consistent with the action of the circulating protein to bind PlGF, free (or unbound) PlGF levels are decreased in preeclamptic women well before the onset of clinical symptoms.⁴⁸ When administered to pregnant and non-pregnant rats, sFlt-1 produces a syndrome of hypertension, proteinuria, and glomerular endotheliosis resembling the human syndrome of preeclampsia. The glomerular lesion in these experimental animals, consisting of severe glomerular endothelial swelling with preserved foot processes in association with heavy proteinuria, is striking in its resemblance to the human counterpart of preeclampsia.⁴⁷

VEGF and PlGF are known to induce the formation of nitric oxide and vasodilating prostacyclins in endothelial cells, decreasing vascular tone and blood pressure. VEGF, synthesized in large amounts by glomerular podocytes, may be important in maintaining the health and healing of glomerular vascular endothelial cells, so that its absence induces proteinuria and glomerular endotheliosis.⁴⁹ It has been shown that VEGF induces endothelial fenestrae *in vitro* and the loss of 50% of VEGF production in the mouse glomerulus leads, not only to glomerular endotheliosis, but also a loss of glomerular endothelial fenestrae.⁴⁹ Antagonists of VEGF, used in anti-angiogenic oncology trials, sometimes produce hypertension and proteinuria in human subjects.⁵⁰ Furthermore, exogenous VEGF and PlGF can reverse the anti-angiogenic effects of preeclamptic blood, as assessed by studies of angiogenesis *in vitro*.⁴⁷ Thus, the anti-angiogenic effects of sFlt-1 may account for many of the manifestations of preeclampsia, including the unique glomerular changes (Figure 2).

The concentration of sFlt-1 starts to rise near the end of the second trimester in women destined to have preeclampsia, a full 4 to 5 weeks before clinical manifestations of this syndrome (eg, hypertension and proteinuria) are first detected.⁴⁸ By the time preeclamptic manifestations are pronounced, plasma concentrations of sFlt-1 are greatly elevated, from 2 to 4 times the levels found in normal pregnancy at similar levels of gestation. It is particularly interesting that levels of sFlt-1 in the plasma also begin to rise at about 4 weeks from term in women with normal pregnancies. Even at term, however, the levels in normal women are well below those obtained in the great majority of preeclamptic patients. The concentration of sFlt-1 in plasma is higher in patients with severe preeclampsia than in those with milder

Figure 2: Schematic outline of the pathogenesis of preeclampsia



disease.^{47,48} In normal pregnancy, circulating concentrations of PlGF rise steadily, reach a peak at about 30 weeks, and then decline. In women in whom preeclampsia develops later, there is a modest, but significant decrease in PlGF levels beginning as early as the first trimester; however, from mid-pregnancy on, the concentration of unbound PlGF in plasma is significantly lower at the time when sFlt-1 levels are rising.^{48,51} Unbound PlGF is also freely filtered into the urine and, thus, may also serve to predict the subsequent development of preeclampsia.⁵²

Speculations about the mechanisms of preeclampsia

If sFlt-1 is an important cause of preeclampsia, there might be at least 2 kinds of predisposing factors. One might involve the overproduction of sFlt-1, such as in multiple gestation, hydatiform mole, trisomy 13, and, possibly, first pregnancy. Another set of predisposing factors would include disorders that sensitize the maternal vascular endothelium to the anti-angiogenic effects of sFlt-1. Such factors might include obesity, preexisting hypertension or renal disease, diabetes, and preexisting vasculitis. We do not yet know whether diabetes, hypertension, and preexisting renal disease predispose to preeclampsia by increasing the production of sFlt-1 or by sensitizing the vascular endothelium to its presence. Hypoxia is known to increase the production of sFlt-1 by placental trophoblasts,⁵³ so that placental ischemia might trigger the preeclamptic syndrome. There is strong evidence for placental ischemia in many patients with preeclampsia, but not in others. Placental infarction, unaccompanied by preeclampsia, is a common finding in mothers with sickle cell anemia and in those with fetuses who have intra-uterine growth retardation. Placental overproduction of sFlt-1, whatever its cause, might decrease angiogenesis locally and result in placental ischemia, thereby initiating a vicious circle leading to even more sFlt-1 production.

Perhaps 3 factors conspire, in variable degrees, to produce the clinical syndrome of preeclampsia:

1) a change in the balance of circulating factors controlling angiogenesis/anti-angiogenesis, attributable to placental overproduction of sFlt-1 and underproduction of PlGF

2) increased vascular endothelial sensitivity to such factors⁵⁴

3) placental ischemia exaggerating the processes described in 1.

Because human pregnancy is initially characterized by rapid angiogenesis localized to the placenta and terminates with regression of blood vessel growth, it is not surprising that, occasionally, systemic manifestations of derangement occur in this remarkable process.

Long-term follow-up of preeclampsia

Considerable evidence suggests that preeclampsia predisposes women to late cardiac and vascular diseases.⁵⁵ Fifteen years after an episode of preeclampsia, the incidence of hypertension is 5 times that found in women with normal pregnancies who never had preeclampsia (37% vs. 7%).⁵⁶ That the tendency to late hypertension is the result of preeclampsia and not inherited is supported by the absence of an abnormal tendency to late hypertension in the siblings of preeclamptic patients.⁵⁶

Peripartum hypertension without proteinuria

This comprises a mixed bag of patients, with several possible etiologies. Some women, usually with a strong family history of essential hypertension, have a normal blood pressure throughout most of their pregnancies. At the end of the third trimester, blood pressure tends to rise to approach the prepregnant level. Usually there is no protein in the urine and the blood uric acid is not elevated. In another group, there is exaggerated sensitivity to the (usually weak) mineralocorticoid effect of progesterone, which produces salt-sensitive hypertension.⁵⁷ In still other patients, the administration of large amounts of intravenous saline during a Caesarean section results in postpartum hypertension and edema that disappears in a few days when the large salt load is excreted. Occasionally, the elevated BP has a psychiatric cause, usually not subtle (eg, the new mother may be deathly afraid of something). Finally, a substantial proportion of patients with gestational hypertension represent an early phase of preeclampsia, in which proteinuria has not yet appeared.

Pre-existing renal disease and pregnancy

If in patients with prior renal disease, the prepregnant BP and serum creatinine are normal, the chances are better than even that preeclampsia can be avoided and, even if not, symptoms are likely to dis-

appear after delivery. If, however, the pre-pregnant serum creatinine is >1.4 mg%, there is at least a 50% chance that renal function will worsen during the pregnancy. In about half of such patients, the decline is not reversed after delivery. If the serum creatinine is >2 mg% before pregnancy, and especially if BP is elevated before pregnancy, the chances are better than even that preeclampsia will complicate pregnancy and that any decline in renal function will not be reversible after the baby is delivered.⁵⁸ These considerations apply, in general, to patients with any kind of renal disease, including patients with transplanted kidneys.⁵⁹

Almost two-thirds of patients with active systemic lupus erythematosus experience a flare of renal signs and symptoms during pregnancy, sometimes progressing to renal failure. On the other hand, successful pregnancy, without renal deterioration, is often accomplished if gestation is started in a period of sustained therapeutic remission of the lupus.⁶⁰ Renal biopsy is usually not necessary during pregnancy. Occasionally, however, especially when the differential diagnosis includes active lupus glomerulonephritis, percutaneous renal biopsy is indicated in order to establish the basis for vigorous treatment of an underlying nephritis with prednisone and other immunosuppressive drugs.

Disclosure: Dr. Karumanchi is a co-inventor on a patent filed by the Beth Israel Deaconess Medical Center for the diagnosis and therapy of preeclampsia. The therapeutic claims of the patent have been licensed to Scios, Inc, CA.

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