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Pregnancy and the Kidney

Renal and Reproductive Functions: *Inextricably Linked*

By Phyllis August

Healthy kidneys—healthy pregnancy

A healthy pregnancy—a baby born at term, with minimal untoward physical consequences to the mother—is the ideal outcome and indeed, when it occurs, is nothing short of a miracle. That the maternal kidneys are such important players in this process is perhaps not news to the seasoned nephrologist, but it is a concept that bears emphasizing, particularly when a woman with kidney disease or even hypertension contemplates pregnancy. Why this should be so is likely a result of the critical role of the kidneys in adapting the circulation to the increasing demands of the conceptus, and accommodating the alterations in blood flow that are necessary for the rapidly enlarging uterus, the growing placenta, and of course the fetus.

Renal-hemodynamic adjustments to pregnancy

The most dramatic renal accommodations to pregnancy include marked vasodilation, increase in glomerular filtration rate (GFR) of 50 percent, and increase in renal blood flow up to 80 percent above baseline. Despite increased GFR and lower blood pressure, there is a cumulative retention of sodium of about 900 mEq, which is a critical step in the generation of the increased plasma volume necessary for perfusion of the growing fetus as well as all other vital organs. These normal physiologic adjustments to pregnancy are barely noticed by the pregnant woman.

There are, however, subtle signs that may be detected on physical and laboratory examination even early in pregnancy. The most noticeable is the early decrease in blood pressure, which in normotensive women results in decrements of about 5–10 mm Hg systolic and 2–5 mm Hg diastolic in comparison with prepregnancy blood pressures. This early pregnancy vasodilation, which becomes even more noticeable in midgestation, is often more apparent in the woman with pre-existing hypertension, in whom decreases in systolic and diastolic blood pressure may be significant enough to permit cessation of antihypertensive therapy during pregnancy.

The mediator(s) of this fairly dramatic phenomenon are not clearly known. “Candidate” vasodilators of pregnancy include estradiol, relaxin, and nitric oxide. Additional consequences are increased cardiac output and increased heart rate secondary to decreased afterload, as well as marked stimulation of all components of the renin-angiotensin-aldosterone system. Without this latter adjustment, women might find it difficult to remain standing for any length of time while pregnant; indeed, a few are prone to syncope.

We demonstrated the importance of the stimulated renin-angiotensin system (RAS) in pregnancy for maintaining normal blood pressure by administering a single dose of captopril to first- and second-trimester normotensive women and observing their blood pres-

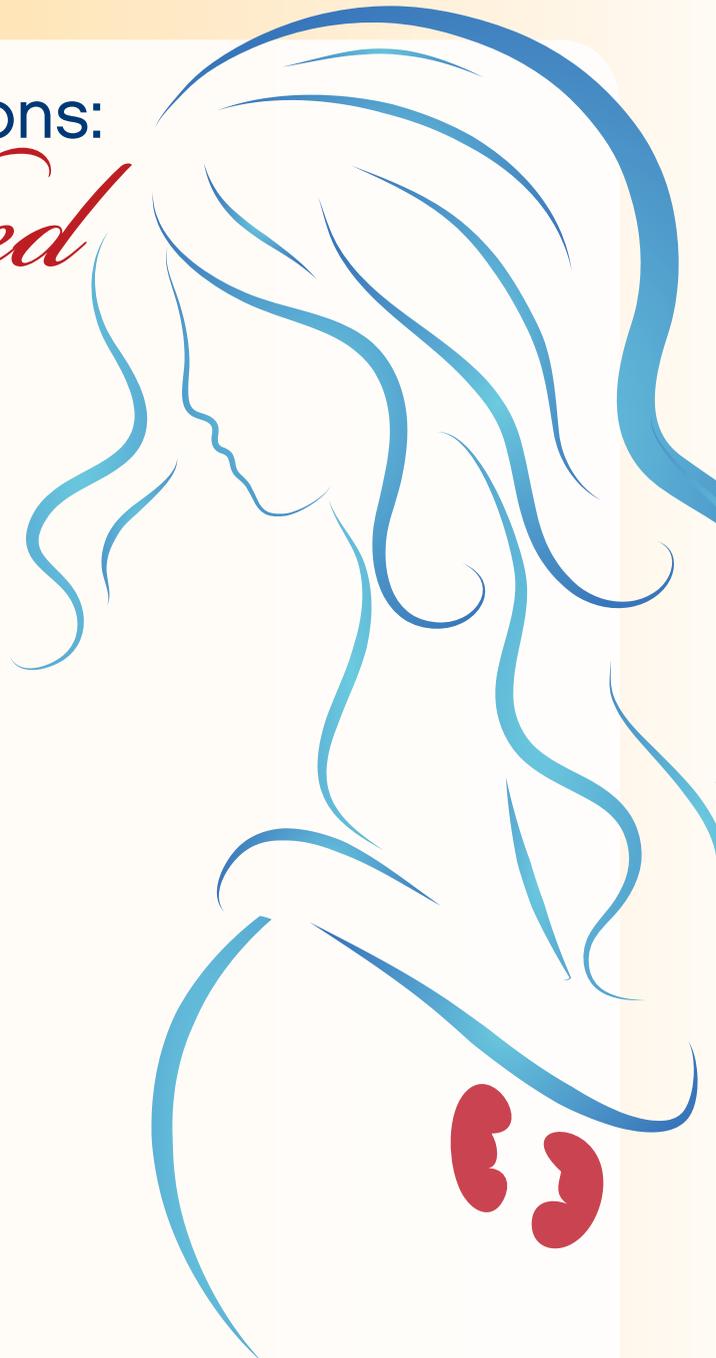
sure and renin responses after 1 hour. In comparison with age-matched nonpregnant women, acute blockade of the RAS system in early pregnancy resulted in significantly greater decreases in blood pressure and compensatory increases in plasma renin activity, suggesting that the stimulated RAS was playing a critical role in supporting blood pressure (1). The increases in GFR and renal blood flow are largely mediated by vasodilation and increased renal plasma flow (2). The results of clinical studies using clearance techniques (inulin, p-aminohippuric acid, and neutral dextrans) suggest that additional factors, such as decreased oncotic pressure and an increased glomerular ultrafiltration coefficient, are also important. Renal blood flow increases more than GFR in early and midpregnancy, and filtration fraction decreases; however, in late gestation, there is an increase in filtration fraction. Thus, there is little evidence for increased intraglomerular pressure and therefore little risk that the hyperfiltration associated with gestation is associated with additional strain on the kidneys (3).

Nonhemodynamic alterations in renal function in normal pregnancy

During pregnancy, there are increases in respiratory rate, tidal volume, and alveolar ventilation, resulting in reduced arterial PCO_2 . This has been attributed to increased progesterone, which stimulates the medullary respiratory center. The partly compensated respiratory alkalosis is detectable by a reduction in hydrogen ion concentration, PCO_2 , and serum bicarbonate. Water metabolism is also altered. There is a decreased osmotic threshold for thirst and arginine vasopressin release during pregnancy, with a decrease in plasma osmolality and serum sodium (4). Levels of 1,25 dihydroxyvitamin D are increased in pregnancy, parathyroid hormone is decreased, and urinary excretion of calcium is decreased (5).

There are other physiologic adjustments in pregnancy that are less well characterized but that may be relevant in women with underlying kidney disease. These include adjustments in inflammation and immunity. The alterations in immunity are in part related to the immunologically privileged status of the fetus. There is also specific maternal tolerance to fetal antigens at the maternal–fetal interface and alterations in circulating immune cell populations and antibodies that may downregulate the maternal immune response (6). Pregnancy has also been characterized as a state of enhanced inflammation, which may be mediated by trophoblast-derived microparticles that are released into the maternal circulation and stimulate the maternal systemic inflammatory response. The subtle increases in leukocyte count, C-reactive protein, and erythrocyte sedimentation rate in pregnant women may be interpreted as signs of increased inflammation (7).

Familiarity with these changes is critical to the accurate interpretation of laboratory results in the pregnant woman, in whom BUN, creatinine, serum sodium, and bicarbonate are usually slightly lower than in normal pregnant women (8).



Women with kidney disease in pregnancy

Given these profound hemodynamic, metabolic, and immunologic alterations that are features of normal healthy pregnancy, it is not surprising that women with kidney disease are at increased risk for pregnancy complications. Although data regarding pregnancy outcomes in women with renal disease are derived mainly from case series rather than from carefully conducted observational studies with control groups, there is consensus that the degree of renal functional impairment at the time of conception is the single most important determinant of both maternal and fetal outcomes.

One such landmark case series, reported in the *New England Journal of Medicine* 15 years ago by Jones and Hayslett, reported that 23 percent of women with a serum creatinine above 2.0 mg/dL at the beginning of pregnancy experienced progression to ESRD within 6 months after delivery (9). When hypertension is present early in pregnancy, the risks to both mother and fetus are considerably higher. Particularly striking is the impact of pre-existing hypertension in the setting of renal disease on the incidence of superimposed pre-eclampsia. The relationship between baseline proteinuria and pregnancy outcome is less clear, perhaps because increases in proteinuria during early pregnancy are usually related to the hemodynamic alterations in pregnancy rather than to progression or worsening of underlying renal histologic features.

Continued on page 8

Renal and Reproductive Functions

Continued from page 7

Specific renal diseases and pregnancy outcome

Evidence supporting a relationship between underlying renal histologic features and pregnancy outcome is lacking. There are, however, a few generalities worth making. Women with diabetic

nephropathy should be counseled to plan pregnancy before they develop macroalbuminuria, given that pregnancy outcomes are significantly better when GFR is preserved and microalbuminuria rather than macroalbuminuria is present. Women with lupus should be in remission for 6 months before conception, and even then, flares of disease are not uncommon during pregnancy.

High titers of antiphospholipid antibodies, and/or presence of the lupus anticoagulant, greatly increase the risk of adverse outcomes, and strong con-

sideration should be given to prophylactic anticoagulation in this setting. Mycophenolate mofetil is a teratogen, and this drug should be withdrawn and women treated with other agents (e.g., azathioprine, cyclosporine, prednisone) well before conception. Cyclophosphamide is also contraindicated in pregnancy. Finally, blockers of the RAS, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and renin inhibitors, should be discontinued before pregnancy, and nephrologists should be aware that cessation of these drugs, as well as the hemody-

namic changes of pregnancy, may be partly if not totally responsible for significant increases in proteinuria that are noted early in gestation. Finally, if the cause of the underlying renal disease is unknown, renal biopsy may be helpful if performed early in pregnancy, particularly in the setting of nephrotic syndrome or reduced renal function, and especially if therapeutic interventions are contemplated.

In summary, the renal adaptation to pregnancy is critical to ensure appropriate volume expansion and increased perfusion to meet the needs of the developing fetus and placenta. Vasodilation, lower blood pressure, and increased cardiac output are the most obvious consequences of this process. Women with kidney disease have diminished capacity to adapt to pregnancy, and the degree to which pregnancy is compromised is related to the degree of renal functional impairment and the degree of hypertension. The treatment of pregnant women with kidney disease is a team effort and involves close monitoring, appropriate blood pressure control, and carefully timed delivery. ●

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