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Review

Pregnancy and The Kidneys: A Brief Systematic Review

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ABSTRACT

Significant anatomical and physiological changes occur in kidneys during pregnancy. These need to be well defined to discriminate real nephrological disorders. Pregnancy may cause a predisposition to some kidney diseases, and it is not surprising that women with already-known kidney disorders may face challenges during this period. Management is more complicated than in the general population as both maternal and fetal health should be considered. In this report, besides anatomical and physiological changes that occur in pregnancy, common nephrological disorders like hypertension, urinary tract infections, and acute and chronic kidney injury are reviewed.

Keywords: Pregnancy, hypertension, urinary tract infection, acute kidney injury, chronic kidney injury

RENAL ANATOMICAL CHANGES IN PREGNANCY

Renal size increases by 1 cm during pregnancy because of increased vasculature and interstitial volume. Physiologic hydronephrosis may occur due to mechanical compression by the enlarging uterus and smooth muscle relaxation related to progesterone. It is commonly more prominent on the right side as the uterus usually undergoes rotation with tilting to the right. Ureteric compression may cause urine stasis which may increase the likelihood of urinary tract infections (UTIs), nephrolithiasis, and pyelonephritis. Loss of bladder tone may cause symptoms like urinary frequency, urgency, and incontinence (1).

RENAL PHYSIOLOGICAL CHANGES IN PREGNANCY

Blood volume increases progressively throughout the pregnancy. Systemic vascular resistance and so the systemic blood pressure decrease. Increased blood volume and reduced systemic vascular resistance accompanied by increased sympathetic activity lead to an increase in heart rate and cardiac output. Systemic vasodilation causes renal vascular dilatation and increased glomerular filtration which causes a reduction in serum creatinine, blood urea nitrogen, and uric acid levels (2). Urinary protein and glucose excretion also increase. Sodium is filtrated and reabsorbed more due to the activated renin–angiotensin–aldosterone system, and sodium retention may contribute to the increased plasma volume (1). Normal plasma osmolality threshold decreases and plasma osmolality becomes 270 to 275 mOsm/kg. A fall in serum sodium level by 5 mEq/L occurs (3).

Changes in the immune system (shift from a T helper cell type 1 to a T helper cell type 2 phenotype and increase in the number of regulatory T cells) occur in pregnancy to establish fetal tolerance. This may impact the behavior of autoimmune diseases (2).

HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (average of at least two measurements) (4,5). Blood pressure should be measured with a validated and calibrated device and with a standardized technique (5). The prevalence of hypertension in pregnancy continues to increase due to advanced maternal age and cardiometabolic risk factors like obesity. It can cause maternal and fetal mortality, and morbidity (4).

Hypertension in pregnancy can be classified as chronic arterial hypertension, preeclampsia

superimposed upon chronic arterial hypertension, gestational hypertension, and preeclampsia.

• **Chronic arterial hypertension** is considered when the hypertension is diagnosed before the 20th week of gestation and/or persists longer than 12 weeks postpartum. These women have an increased risk for superimposed preeclampsia and other maternal complications like heart failure, stroke, pulmonary edema, acute kidney injury (AKI) or death, and fetal complications like intrauterine growth retardation, placental abruption, preterm delivery, and fetal loss (2,3,6). Physiologic decrease in blood pressure may mask hypertension in early pregnancy (2).

• **Preeclampsia superimposed upon chronic arterial hypertension** is considered in the presence of worsening hypertension with new-onset proteinuria and/or significant new end-organ dysfunction after 20 weeks of gestation in a patient with chronic hypertension. Maternal and fetal morbidities increase with superimposed preeclampsia (7).

• **Gestational hypertension** is considered when pregnant patients had high blood pressure after the 20th week of gestation. Blood pressure normalizes in the postpartum period (2). These women have an increased risk for superimposed preeclampsia. Blood pressure usually resolves after 12 weeks in the postpartum period (3).

• **Preeclampsia** is considered in the presence of new-onset hypertension after 20 weeks of gestation and urinary protein excretion ≥ 300 mg/d or urine protein/creatinine ratio (UPCR) ≥ 0.3 g/g (2). Risk factors for preeclampsia are shown in **Table 1**. The amount of proteinuria is not associated with maternal or fetal outcomes (7). In the absence of proteinuria clinical features of severity (**Table 2**) may help diagnosis (2). Serum uric acid is often greater than expected.

Table 1. Risk factors for preeclampsia (3)

•Advanced maternal age
•Nulliparity
•Being pregnant with more than one baby
•Preeclampsia in a previous pregnancy
•Family history of preeclampsia
•Chronic hypertension
•Diabetes mellitus
•Chronic kidney disease
•Autoimmune disease
•>10 years since the previous pregnancy
•Obesity

Table 1. Clinical features of severity (7)

•Thrombocytopenia (Platelets < 100000/μL)
•Renal insufficiency (Serum creatinine >1.1 mg/dL or doubling of serum creatinine concentration in the absence of another kidney disease)
•Impaired liver function (Liver transaminases 2× upper limits of normal)
•Pulmonary edema
•New-onset cerebral or visual symptoms

HELLP (Hemolysis, Elevated liver enzymes, Low Platelets) syndrome is a subtype of preeclampsia with hemolysis (microangiopathic blood smear; schistocytes and burr cells, serum bilirubin ≥1.2 mg/dL, low serum haptoglobin or lactate dehydrogenase ≥2 times the upper level of normal), elevated liver enzymes (≥2 times the upper level of normal), and thrombocytopenia (<100,000 cells/microL) (8).

Eclampsia develops when a seizure occurs in a preeclamptic patient (9).

Preeclampsia is associated with later-life cardiovascular risk. Patients who had preeclampsia should receive counseling before their next pregnancy (7).

Maternal benefits of lowering blood pressure and the potential fetal risks due to reductions in uteroplacental circulation should be considered (4,10). Lowering blood pressure aggressively is usually not recommended (4). Bed rest or salt restriction was not shown to reduce preeclampsia risk (11). Treatment should be initiated usually when the blood pressure is ≥150-160/100-110 mmHg (2). Target blood pressure is usually accepted as <140/90 mmHg (3,6).

Oral nifedipine, oral/intravenous labetalol, or intravenous hydralazine may be used for severe hypertension (≥170/110 mmHg). Methyldopa, labetalol, and long-acting nifedipine are oral antihypertensive agents that may be used for non-severe hypertension in pregnancy (5). Diuretics are not preferred as they may cause volume depletion, and angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), renin inhibitors, and mineralocorticoid receptor antagonists are contraindicated as they are teratogenic (7).

Delivery is the preferred treatment for preeclampsia, especially after 37 weeks of gestation, and for the ones with severe clinical features (2). Maternal and fetal conditions should be considered in the delivery decision. Corticosteroids should be administered between 25 and 34 weeks to decrease the risk of respiratory distress syndrome in infants (3).

Magnesium sulfate is used in the treatment and prevention of eclampsia (5).

Low-dose aspirin is recommended to prevent preeclampsia in high-risk patients, and preferably should be initiated before 16 weeks of gestation (5,12). Oral calcium supplementation (500 mg/d) may be suggested for women with poor dietary intake of calcium (<900 mg/day) to prevent preeclampsia (5).

URINARY TRACT INFECTIONS IN PREGNANCY

UTIs are common in pregnancy and are classified as lower UTIs (asymptomatic bacteriuria or acute cystitis) and upper UTIs (acute pyelonephritis). Enterobacteriaceae and Escherichia coli are responsible for most of the cases (13).

•Asymptomatic bacteriuria is diagnosed when a urine sample shows 10^5 colony-forming units (CFU)/mL without symptoms of UTI ideally in two consecutive urine cultures. In pregnant women, asymptomatic bacteriuria should be treated as it can turn to symptomatic acute cystitis or even pyelonephritis and can increase the risk for adverse fetal outcomes (preterm birth, low birth weight, and perinatal mortality) (13).

•Symptoms like frequency, dysuria, or strangury may indicate acute cystitis. 10^2 organisms/ml is sufficient to diagnose the presence of pyuria and symptoms (13).

•Symptoms like fever, dysuria, and loin pain may indicate acute pyelonephritis with generally more than 10^5 organisms/ml in the urine (3,14).

Management of UTIs in Pregnancy

Penicillins (with or without beta-lactamase inhibitors), cephalosporins, aztreonam, and fosfomycin are generally accepted as safe in pregnancy. Supportive treatment and intravenous antibiotics (preferably broad-spectrum beta-lactams) should be administered for acute pyelonephritis (14).

Antibiotic prophylaxis is suggested for the ones who have persistent bacteriuria. Prophylaxis should be considered in patients with recurrent UTI (2 episodes during pregnancy) (3).

ACUTE KIDNEY INJURY

Pregnancy-related AKI may cause maternal and fetal morbidity and mortality (15). Pregnancy-related AKI increases the risk of preterm births, low birth weights, and neonatal intensive care unit admissions (16). Older maternal age, preeclampsia, antepartum/postpartum haemorrhage, infections (eg; sepsis) lower socioeconomic status, obesity, and comorbidities like diabetes, hypertension, and chronic kidney disease are the risk factors for AKI in pregnancy (15-17).

Pregnancy-related AKI is not well defined. Serum creatinine usually decreases below 0.8 mg/dL in pregnancy. Therefore, even a seemingly normal creatinine may be indicative of pregnancy-related AKI (16). Serum creatinine checked in early pregnancy may help the diagnosis of AKI later on (15,16).

Prerenal, renal, and postrenal causes should be sought. In the first trimester, volume depletion due to hyperemesis gravidarum may cause prerenal AKI (16). Hemorrhage, pulmonary embolism, heart failure, or sepsis are some of the other reasons that may cause prerenal AKI, and these may also result in ischemic acute tubular necrosis if the injury is severe. Acute fatty liver of pregnancy, amniotic fluid embolism or severe preeclampsia, and HELLP syndrome may cause acute tubular necrosis. Severe hypotension may result in acute cortical necrosis (2). Postrenal AKI may be more common in the second and third trimesters due to the compression of the gravid uterus on the ureter (16).

Urinalysis, urine microscopy, comprehensive metabolic panel, coagulation panel, and serological work may help with differential diagnosis. Serum complement levels may be found elevated due to increased synthesis by the liver in pregnancy. A kidney ultrasound may be used to exclude postrenal etiologies (16). Renal biopsy may be considered in the first and second trimesters if the diagnosis is needed for urgent therapy (18).

Supportive care and specific treatment options (if a specific cause of pregnancy-related AKI is defined) should be administered (16). Dialysis may be required in some patients, and it is associated with increased mortality (2).

Pregnancy-related AKI may increase the risk of hypertension CKD in long term (11,16).

CHRONIC KIDNEY INJURY

Pregnant patients with chronic kidney injury (CKD) may have fetal or maternal complications including preeclampsia, preterm delivery, low birth weight, deterioration in kidney functions, and increased mortality. (19) Fertility rate is lower in patients with more advanced kidney disease (3). The higher the stage of CKD, the greater the risk of adverse pregnancy outcomes. Glomerular nephropathies, autoimmune diseases, and diabetic nephropathy may have poorer outcomes. CKD increases the risk of preeclampsia and hypertension in pregnancy (11).

Euvolemia should be aimed to avoid dehydration and pulmonary edema. Thromboprophylaxis with low molecular weight heparin is recommended for patients with nephrotic-range proteinuria if there is no contraindication. In the presence of additional risk

factors, thromboprophylaxis may also be considered for patients with non-nephrotic range proteinuria. Anemia can be treated with parenteral iron and erythropoietin-stimulating agents if indicated. Vitamin D supplementation is also suggested for patients who have vitamin D deficiency. Non-calcium-based phosphate binders and calcimimetics should be discontinued. Maternal urea concentration, gestation, renal function trajectory, fluid balance, biochemical parameters, blood pressure, and symptoms of uremia should be all considered when taking the decision about dialysis initiation (19).

If patients with the end-stage renal disease get pregnant, their dialysis treatment should be intensified (frequency and duration) (11). Dialysis duration should be more than 20 hours/week to maintain serum urea nitrogen target near-normal (<50 mg/dL). Residual renal function should also be considered. Although a successful pregnancy is possible for patients under peritoneal dialysis or hemodialysis perinatal mortality and preterm delivery may be more common. Pregnancy may cause the formation of anti-HLA antibodies which may be a problem to find a suitable kidney donor in the future (2).

Fertility improves after renal transplantation. Risks for pregnancy complications are also lower in comparison to dialysis patients (2). Renal transplant patients are usually advised to wait at least 1 year for stable graft function before pursuing pregnancy. Immunosuppressive treatment should be arranged. Prednisolone, azathioprine, and tacrolimus/cyclosporine are the immunosuppressive agents preferred (2). Renal transplant patients have a higher risk of complications than in the general population (11). Mycophenolate should be withdrawn 3-6 months before conception. Aspirin is suggested to prevent preeclampsia (19).

SPECIFIC RENAL DISEASES IN PREGNANCY

Specific renal diseases like diabetic nephropathy, lupus nephritis, and vasculitis, reflux nephropathy, congenital abnormalities of the kidney and urinary tract (CAKUT), and glomerulonephritis are not reviewed in this report.

DISCLOSURES

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