

Gynaecologic Nephrology

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Abstract: Renal issues are commonly encountered in females. They can occur both in pregnant and nonpregnant females. Many physiologic changes occur during pregnancy to accommodate the growing fetus. Pregnancy is characterized by changes in blood pressure and expansion of total body volume which results in high glomerular filtration rate. The common renal problems seen in pregnant females are hypertension, proteinuria with or without nephrotic syndrome, acute kidney injury. It is not uncommon to see a pregnant female who may have pre-existing chronic kidney disease. A very few women receiving dialysis become pregnant. Renal transplantation restores the infertility seen in chronic kidney disease. Renal transplant recipients with pregnancy require very close monitoring of immunosuppressive medications to prevent acute rejection due to altered drug absorption and metabolism in pregnancy. Uterine fibroids are commonly encountered in women of reproductive age. Nonpregnant females with uterine fibroids usually experience non-renal symptoms like excessive uterine bleeding but few of them can develop hypertension, acute kidney injury and chronic kidney disease from uterine fibroids. Malignancies of female genital system can give rise to kidney failure when locally invasive. This review paper gives details of various renal problems seen by nephrologists in female patients both during pregnancy and nonpregnant states in daily practice.

Key words: Pregnancy, Uterine Fibroids, Renal Disease, Glomerular Filtration Rate (GFR), Vascular Endothelial Growth Factor (VEGF), Acute Kidney Injury Network (AKIN)

INTRODUCTION

A-renal disorders during pregnancy: This section will first review physiologic changes during pregnancy and then various disorders seen by nephrologists during pregnancy.

Renal physiology in pregnancy: Pregnancy is accompanied by many changes in the urinary tract. Both kidneys increase in size by 1-1.5 cm during pregnancy due to increase in renal vascular and interstitial volume (Bailey and Rolleston, 1971). There are no histological changes in the kidney but glomerular filtration rate increases.

The ureters and renal pelvis undergo dilatation in many pregnant women under effect of progesterone particularly in primigravida (Rasmussen and Nielsen, 1988; Beydoun, 1985). This dilatation is more prominent on right side than the left. The dilated collecting system can hold 200-300 cc of urine. This dilatation of urinary tract is visible on renal ultrasound by the second trimester and can persist up to 12 weeks postpartum. Urinary bladder becomes edematous and

hyperemic during pregnancy. Progesterone causes relaxation of the wall of the bladder which may lead to its increased capacity. The bladder can be displaced superiorly and anteriorly by the enlarged gravid uterus. Due to relaxation of bladder smooth muscles, there is incompetence of the vesicoureteral valve and it can result in intermittent vesicoureteral reflux (Mattingly and Borkowf, 1978; Heidrick *et al.*, 1967). Pregnant women experience increased urinary frequency, nocturia, dysuria, urgency and stress incontinence (Thorp *et al.*, 1999; Wesnes *et al.*, 2007).

Glomerular Filtration Rate (GFR) increases in pregnancy due to rise in cardiac output and renal flow rate. Total peripheral vascular resistance decreases during pregnancy due to vasodilatation. It results from decreased responsiveness of vascular endothelium to vasoconstrictors (angiotensin, epinephrine and vasopressin) and increased production of vasodilators like nitric oxide. Blood volume increases in pregnancy due to activation of renin angiotensin system causing salt and water retention (Elsheikh *et al.*, 2001). Total body water increases by 6-8 L leading to expansion of plasma and interstitial volumes. The increase in GFR

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occurs within one month of the conception and reaches its peak in early second trimester. GFR increases usually by 40-50% over baseline and decreases slightly toward term (Davison and Dunlop, 1980).

Serum creatinine decreases during pregnancy due to high GFR and is usually 0.4 mg dL⁻¹ lower than pre-gestation level. Renal function is usually monitored during pregnancy by measurement of serum creatinine. Normal value of serum creatinine during pregnancy is 0.4-0.6 mg dL⁻¹. Thus, a pregnant woman with serum creatinine of 1.0 mg dL⁻¹ has significant impairment of renal function. 24 h urine collection for creatinine clearance is of limited accuracy in pregnancy (Cote *et al.*, 2008). Urinary protein excretion increases in normal pregnancy to 200 mg day⁻¹ in the third trimester due to rise in GFR. Serum uric acid declines in early pregnancy due to rise in GFR. It can be as low as 2-3 mg dL⁻¹ by 24 weeks of gestation (Lind *et al.*, 1984). After 24 weeks, uric acid level begins to rise and can reach non gestation level by term. Rise in serum uric acid in early pregnancy points to presence of renal disease. Hyperuricemia is frequently encountered in patients with preeclampsia.

Certain electrolyte and acid base changes can also be appreciated during pregnancy. Hyponatremia is frequently encountered in pregnancy. Serum sodium level is usually around 132-134 meq L⁻¹ (Lindheimer *et al.*, 1989). Hyponatremia is usually due to effect of relaxin on the brain. The ability to maintain osmoregulation via thirst and anti-diuretic hormone level is well maintained in pregnancy. Pregnant women suffer from chronic respiratory alkalosis due to increase in minute ventilation. This hypocapnia results from direct stimulation of respiratory center by progesterone (Lim *et al.*, 1976). Partial pressure of carbon dioxide (pCO₂) decreases to 27-32 mm.Hg and is accompanied by compensatory increase in renal excretion of bicarbonate. There is small reduction in serum anion gap in pregnant women and can be detected throughout the pregnancy (Akbari *et al.*, 2007). Tubular function in pregnancy is impaired and it manifests as glucosuria, aminoaciduria and increased urinary excretion of beta microglobulin. Placenta produces an enzyme, vasopressinase, which degrades vasopressin produced by pituitary gland. Increased activity of this enzyme can give rise to diabetes insipidus in some pregnant women. Table 1 classifies various renal problems seen commonly by nephrologists regarding female reproductive system.

Now this section will review various renal issues seen in pregnancy.

A-hypertensive disorders in pregnancy: Normal pregnancy is characterized by drop in blood pressure due to decrease in peripheral vascular resistance which results from generalized vasodilatation.

Table 1: Classification of renal disorders of female reproductive system

Renal disorders of Female Reproductive System	
<u>During Pregnancy</u>	
A-Hypertensive disorders of pregnancy	1-Chronic hypertension
	2-Gestational hypertension
	3-Preeclampsia
4-Preeclampsia superimposed on preexisting hypertension	
B- Diabetes Insipidus	
C- Acute Kidney Injury	
D -Chronic Kidney Disease in pregnancy	
E-Pregnant Patient with End Stage Renal Disease	
F -Renal Transplant Recipient with pregnancy	
<u>In Non Pregnant Females</u>	
A-Uterine fibroids and malignancies of female reproductive system	1-Urinary Retention
2-Acute Kidney Injury	3-Chronic Kidney Disease
	4-Hypertension

This is usually evident by 6 weeks of gestation and leads to an average drop in blood pressure of 10mm.Hg below non-pregnant levels by second trimester. Some pregnant women can develop hypertension during pregnancy. These hypertensive disorders are divided into four categories (Helewa *et al.*, 1997). They are discussed below.

Chronic hypertension: It is presence of high systolic and diastolic blood pressure before onset of pregnancy or is present before 20th week of pregnancy at least on two occasions. It can persist longer than 12 weeks after delivery of the baby. Usually systolic blood pressure is >140 mm.Hg and/or diastolic blood pressure is >90 mm.Hg. Chronic hypertension can occur as result of number of medical disorders or can occur without any cause as idiopathic hypertension. Chronic hypertension is present in 3-5% of pregnancies (Yoder *et al.*, 2009; Magee *et al.*, 1999). It is more common in obese, blacks and older maternal age. Pregnant women with chronic hypertension have an increased risk of preeclampsia and preterm delivery.

Gestational hypertension: It is new onset of hypertension in a previously normotensive pregnant female which occurs in last trimester of pregnancy usually around 32 weeks of pregnancy. It can occur in up to 6% of pregnancies (Yoder *et al.*, 2009). There is no proteinuria and hypertension resolves usually by 12 weeks after delivery of the baby. Therefore reassessment at 12 weeks postpartum is required to make definite diagnosis. If hypertension persists after 12 weeks in postpartum period, the diagnosis is usually preexisting chronic hypertension which was masked in early during pregnancy due to vasodilatation. Gestational hypertension can recur in subsequent pregnancies (Hjartardottir *et al.*, 2006). Gestational hypertension can progress to overt preeclampsia in 10-25% of cases (Wallis *et al.*, 2008; Saudan *et al.*, 1998).

Table 2: Risk factors for preeclampsia

Social and demographic Factors	Medical Factors
Age <18 years or >40 years	Preeclampsia in previous pregnancy
Black race	Family history of preeclampsia
Woman with high body mass index	Chronic hypertension
Male partners whose mother or previous partner had preeclampsia	Chronic renal disease
Nulliparity	Vascular or connective tissue disease
Prolonged inter-pregnancy interval	Diabetes Mellitus
Partner related factors (new partner, limited sperm exposure such as with use of barrier contraception)	Hydrops fetalis
	Multifetal gestation
	Hydatidiform mole
	Genetic predisposition
	Antiphospholipid antibody syndrome or inherited thrombophilia
	Unexplained fetal growth restriction

Preeclampsia: It is defined as new onset of hypertension and proteinuria in a previously normotensive pregnant woman after 20 weeks of gestation. It can rarely occur before 20 weeks of gestation as seen in molar pregnancy. Preeclampsia is usually classified as mild or severe preeclampsia.

Eclampsia is characterized by onset of grand mal seizures in a woman with preeclampsia. The patient usually does not have any pre-existing history of any other neurologic conditions.

HELLP syndrome is severe form of preeclampsia and is characterized by hemolysis, elevated liver enzymes and low platelets. It can occur independent of presence of proteinuria and hypertension in 15-20% of patients (Reubinoff and Schenker, 1991).

Incidence of preeclampsia: Preeclampsia is seen in 7.5% of pregnancies throughout the world (Dolea and AbouZahr, 2003). Incidence varies depending upon maternal age and ratio of primigravida among populations (Hutchison *et al.*, 2003). In the United States, preeclampsia and eclampsia account for 15-20% of all pregnancy related maternal mortality.

Risk factors for preeclampsia: A number of conditions can predispose pregnant woman to develop preeclampsia. These risk factors can be divided into social, demographic and medical risk factors (Table 2).

Pathogenesis of preeclampsia: Placenta plays a central role in pathogenesis of preeclampsia since delivery of placenta is associated with remission of the disease (Shembrey and Noble, 1995). Fetus is not needed for preeclampsia as preeclampsia can occur in case of hydatidiform mole. During early placental development fetal cytotrophoblast invades the uterine spiral arteries of the decidua and myometrium which results in their transformation from small resistance uterine vessels into flaccid low resistance, high caliber capacitance vessels (Wolf *et al.*, 1980). This vascular transformation allows increase in uterine blood flow needed to sustain the fetus through pregnancy. This

transformation is incomplete in preeclampsia (Robertson *et al.*, 1967). Cytotrophoblast invasion of the arteries remains limited to superficial decidua and myometrial segments remain narrow and undilated (Meekins *et al.*, 1994). In normal pregnancy, the developing cytotrophoblasts acquire endothelial cell surface adhesion phenotype called dubbed pseudovasculogenesis (Zhou *et al.*, 1997). Certain angiogenic and antiangiogenic factors and receptors expressed by cytotrophoblast play a key role in the placental pseudovasculogenesis like Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PlGF), soluble FMS-like tyrosine kinase 1 (sFlt) which is also referred to as soluble VEGF receptor 1 (sVEGFR1), Endoglin (a truncated form of a TGF – beta receptor) and angiopoietin receptors TIE-1 and TIE-2. The local balance of these factors is of paramount importance in placental vasculogenesis. VEGF ligands and receptors are highly expressed by placental tissue in the first trimester (Yancopoulos *et al.*, 2000). sFlt decreases cytotrophoblast invasiveness *in vitro* (Zhou *et al.*, 2002). sFlt levels are very low in early pregnancy and rise towards end of pregnancy signaling termination of placental vasculogenesis. In preeclamptic women, sFlt levels are elevated very early during pregnancy and contribute to inadequate cytotrophoblast invasion in preeclampsia as seen in primigravida and twin pregnancies (Wolf *et al.*, 2005; Bdolah *et al.*, 2008). VEGF is important in the health of fenestrated and sinusoidal endothelium found in renal glomerulus, brain and liver, these organs are particularly affected in preeclampsia (Esser *et al.*, 1998). VEGF is highly expressed by podocytes and glomerular endothelial cells (Simon *et al.*, 1998). High circulating levels of sFlt in preeclampsia bind VEGF and PlGF in circulation leading to their decreased serum levels interfering with placental vasculogenesis and hence cause placental insufficiency.

Pathology: Renal pathology in preeclampsia is characterized by endothelial swelling called glomerular endotheliosis in which endothelial cells become swollen,

develop vacuolization and lose their fenestrae. There is deposition of fibrinogen and fibrin within and under the endothelial cells. The podocyte foot processes are intact early during the disease but podocyturia is seen in preeclampsia and other high risk pregnancies (Jim *et al.*, 2012). This glomerular endotheliosis is not pathognomonic to preeclampsia. Renal blood flow and GFR are low in preeclampsia due to high renal vascular resistance and decrease in ultrafiltration coefficient of glomerular capillaries due to endotheliosis. Systemic vasoconstriction results in high blood pressure. Women with preeclampsia have endothelial dysfunction which is present prior to onset of hypertension and proteinuria (Khan *et al.*, 2005). This endothelial dysfunction persists for many years after preeclampsia (Chambers *et al.*, 2001).

Long term epidemiological studies have shown increased prevalence of hypertension, diabetes mellitus, ischemic heart disease, ESRD, stroke and cardiovascular mortality in women with history of preeclampsia (McDonald *et al.*, 2008; Bellamy *et al.*, 2007).

Clinical features: Preeclampsia is characterized by hypertension which can be mild or severe, proteinuria >300mg/day in 24 h urine collection, edema and hyperuricemia. The degree of proteinuria can vary and range from minimal to nephrotic range proteinuria. Preeclampsia is classified as mild or severe. Patient with proteinuria >5grams per day is classified as severe preeclampsia. Hyperuricemia results from increased tubular reabsorption of uric acid.

Preeclampsia can progress from mild asymptomatic disease to life threatening illness called eclampsia and HELLP syndrome (an acronym for the syndrome of hemolytic anemia, elevated liver enzymes and low platelets). Clinical and laboratory findings help monitoring progression to severe disease. Severe hypertension (BP >160/110 mm.Hg), nausea, vomiting, headaches, visual disturbances, altered mental status and parameters of fetal growth restriction should alarm to presence of severe preeclampsia. Pulmonary edema can occur in 2-3% of severe preeclampsia (Tuffnell *et al.*, 2005). Seizures can occur in 2% of preeclamptic cases (Saftlas *et al.*, 1990). Right upper quadrant pain or epigastric pain can point to liver injury. Laboratory findings include hemoconcentration, microangiopathic hemolytic anemia with elevated bilirubin and low haptoglobin levels, thrombocytopenia with platelet count <100,000, elevated liver enzymes, high serum creatinine and severe proteinuria >5 gram/day. In 10-15% of women with HELLP and severe eclampsia, it can occur without hypertension or proteinuria.

Treatment of preeclampsia: It includes absolute bed rest, prevention of seizures and prompt control of blood

pressure if BP >150-160/100-110 mm.Hg) to reduce risk of cerebral hemorrhage (ACOG, 2002). The commonly used anti-hypertensive medications include calcium channel blockers, hydralazine and alpha methyl dopa. Use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics and beta blockers should be avoided. Other modalities to treat preeclampsia include administration of magnesium intravenously to prevent seizures. Serum magnesium levels should be monitored to avoid toxicity. The delivery of the baby depends on gestational period and signs and symptoms of severe preeclampsia. Termination of pregnancy is advisable in severe preeclampsia presenting prior to 24 weeks due to high maternal complication rate (Bombrys *et al.*, 2008). In mild preeclampsia presenting between 24-34 weeks of gestation without any signs and symptoms, delivery can be postponed to allow for fetal maturity (Odendaal *et al.*, 1990). Any woman with HELLP syndrome usually needs prompt delivery of the baby due to very high incidence of maternal complications. Intravenous steroids may be used for fetal maturity.

Some modalities for prevention of preeclampsia in high risk women include use of anti-platelet agents, calcium supplementations and use of antioxidants.

Preeclampsia superimposed on chronic hypertension:

It is defined as onset of proteinuria and worsening blood pressure after 20 weeks of gestation in a woman with pre-existing hypertension. The diagnosis of superimposed preeclampsia can be very difficult. In absence of underlying renal disease, the new onset of proteinuria (>300 mg/day) along with worsening hypertension can be defined as superimposed preeclampsia. In patients with preexisting proteinuria, a significant increase in blood pressure >30mm.Hg over baseline along with other clinical and laboratory features such as high levels of liver function tests, thrombocytopenia and hemolysis signify preeclampsia. Treatment is on the same principles as discussed for preeclampsia.

Secondary hypertension in pregnancy:

Hypertension in pregnancy can occasionally be due to causes like renal artery stenosis, primary hyperaldosteronism, hyperthyroidism and pheochromocytoma. Renal artery stenosis is usually fibromuscular in origin in most young pregnant females but atherosclerotic lesions may account for renal artery stenosis in older females. Diagnosis is suspected by presence of treatment resistant hypertension and can be confirmed by magnetic resonance imaging. It is usually treated with angioplasty and stent placement during second and third trimester of pregnancy (Hayashida *et al.*, 2005).

Table 3: Types of Diabetes Insipidus (DI) during Pregnancy

Type of DI	Mechanism of DI	Treatment of DI	Special Features
Gestational diabetes insipidus	Increased vasopressinase activity	Desmopressin either nasally or subcutaneously	Does not recur in subsequent pregnancies
Subclinical central or nephrogenic Diabetes Insipidus	Insufficient vasopressin level or resistance to endogenous vasopressin	Can be treated with vasopressin analogs if central diabetes insipidus	Symptoms present prior to and after pregnancy
DI associated with hepatic dysfunction	Decreased degradation of vasopressinase by hepatic dysfunction resulting in increased activity of vasopressinase	Desmopressin can be given for treatment since it is resistant to degradation by vasopressinase	Usually seen in patients with preeclampsia and HELLP syndrome
Miscellaneous	Deficiency of vasopressin	Responds to administration of vasopressin analogs	Usually occurs in postpartum period due to severe bleeding causing panhypopituitarism

Pheochromocytoma can be associated with high maternal and neonatal morbidity and mortality but usually is diagnosed at time of delivery due to onset of severe hypertensive crisis. Management involves timely attention to blood pressure control and surgery of the tumor is usually postponed after delivery if possible.

Primary hyperaldosteronism in pregnancy is usually suspected by presence of hypokalemia with hypertension. It can be due to presence of either an adrenal adenoma or bilateral adrenal hyperplasia. Circulating progesterone level can antagonize the hyperaldosteronism but it does not occur in every pregnant female necessitating treatment in others (Wyckoff *et al.*, 2000). Surgical resection of the adrenal adenoma is usually deferred until after delivery.

Another cause of secondary hypertension during pregnancy is mineralocorticoid receptor mutation which is very rare. This disorder is caused by mineralocorticoid receptor activation by circulating progesterone during pregnancy and results in marked elevation of blood pressure during pregnancy. Usually, there is no proteinuria or other features of preeclampsia in affected females (Geller *et al.*, 2000). Use of spironolactone can make control of blood pressure worse.

B-diabetes insipidus: aPregnancy is associated with changes in urinary frequency and nocturia. Rarely, polyuria (urine output more than 3L/day) is encountered in pregnancy. Diabetes Insipidus is a rare occurrence in pregnancy and is characterized by polyuria and polydipsia (Durr, 1987). There are various causes of diabetes insipidus during pregnancy (Table 3).

a-Gestational diabetes insipidus: The incidence of diabetes insipidus is 2-4 cases per 100,000 gestations. Diabetes insipidus occurs due to increased degradation of Anti-Diuretic Hormone (ADH) by vasopressinase, an enzyme released from placenta (Durr *et al.*, 1987; Lindheimer *et al.*, 1991). ADH increases permeability of collecting tubules of the kidney to water. This is mediated through effect of ADH on V2 receptors located on renal collecting tubules resulting in formation of concentrated urine. ADH is metabolized by an enzyme called vasopressinase released by

placenta during pregnancy (Durr *et al.*, 1987). Vasopressinase activity increases during pregnancy peaking in the third trimester, remains high during labor and becomes undetectable after delivery of the baby in two to four weeks. Metabolic clearance of ADH increases four to six fold because of increased vasopressinase activity. Plasma ADH level remains normal in most pregnant females besides increased vasopressinase activity due to compensatory increase in pituitary gland production of ADH. As a result of which polyuria is not usually encountered during pregnancy.

Gestational DI usually presents in third trimester of the pregnancy with polyuria, polydipsia (Brewster and Hayslett, 2005). It can occur in postpartum period especially if fluid intake of the patient is restricted which can result in severe hypernatremia (Sherer *et al.*, 2003). It commonly occurs in women with multiple gestations due to higher placental volume and hence increased vasopressinase level. Diagnosis is made by inappropriately low urinary osmolality and high to normal plasma sodium concentration (Durr and Lindheimer, 1996; Davison *et al.*, 1990). Hypernatremia is not usually encountered unless there is limited access to water (Brewster and Hayslett, 2005). Hypernatremia if present due to DI can be dangerous to both the mother and fetus. Gestational DI usually does not recur in subsequent pregnancies.

Treatment of Gestational DI includes administration of desmopressin which can be given either intranasal or subcutaneously. Desmopressin is a vasopressin analog which is resistant to degradation by placental vasopressinase. Usually a dose of 5-20 mcg

Intranasal or 2-5 mcg subcutaneously every 12-24 h is recommended for treatment of DI during pregnancy. dDAVP has no maternal or fetal adverse effects. Usually fluid restriction to 1L/day is advised to avoid hyponatremia from dDAVP.

Subclinical central or nephrogenic DI: This type of diabetes insipidus occurs due to pre-existing insufficient vasopressin level or inability to respond to vasopressin due to various reasons (Iwasaki *et al.*, 1991). Usually, these patients have polyuria and

polydipsia prior to pregnancy and their symptoms continue after delivery of the baby. This type of diabetes insipidus recurs in future pregnancies.

Diabetes Insipidus associated with hepatic dysfunction: It is usually seen in women with preeclampsia, HELLP syndrome, or acute fatty liver of pregnancy and is caused by high circulating levels of vasopressinase (Katz and Bowes, 1987; Ferrara *et al.*, 1980). These women have no prior history of water imbalance. The symptoms of polyuria and polydipsia respond well to administration of desmopressin.

Miscellaneous causes of diabetes insipidus: Some other causes of diabetes insipidus include absolute deficiency of vasopressin which can occur due to severe hemorrhage at delivery resulting in panhypopituitarism. There is concomitant deficiency of other pituitary hormones requiring hormone replacement therapy.

Acute kidney injury in pregnancy: Acute Kidney Injury (AKI) during pregnancy is very rare in developed countries at present. The low incidence in last 40 years is attributed to various factors like safe abortion, more common use of antibiotics and improvement in overall prenatal care. AKI is historically defined as deterioration of renal function over a span of few h to days resulting in retention of nitrogenous products and inability of the kidneys to maintain fluid and electrolyte balance. Serum creatinine declines during pregnancy due to hypervolemia and hyperfiltration (Conrad, 1992). Serum creatinine is usually 40% lower during pregnancy compared to pre-gestation value. This fact should be kept in mind when dealing with a pregnant female with change in renal function during pregnancy. Acute Kidney Injury Network (AKIN) has classified kidney injury into three stages depending upon change in serum creatinine and urine output occurring over 48 h (Table 5). AKIN criterion has not been validated in pregnancy but is used to classify severity of AKI during pregnancy. Both MDRD and Cockcroft- Gault equation are inaccurate for calculation of GFR in pregnant females (Smith *et al.*, 2008; Alper *et al.*, 2007).

AKI in pregnancy can be divided into pre-renal, renal and post renal AKI. Prerenal AKI remains most common form of AKI during pregnancy and is usually caused by hypovolemia and decreased renal perfusion. This occurs with repeated vomiting due to hyperemesis gravidarum or acute pyelonephritis. If uncorrected, prerenal can progress to intrinsic renal disease resulting in ATN. Adequate and immediate correction of renal perfusion is of utmost importance to prevent intrinsic renal disease from prerenal causes. Diagnosis of pre-renal AKI is based on history, physical examination and

laboratory values. Urinalysis can help in differentiating various categories of AKI. Low urinary sodium (less than 20 meq/L), low fractional excretion of sodium (FeNa) <1%, bland urine sediment and high blood urea nitrogen to creatinine ratio (normal ratio being 10-15:1) suggest diagnosis of pre-renal AKI in context of history and physical examination suggestive of hypovolemia.

Renal causes of AKI include acute tubular necrosis (ATN), bilateral cortical necrosis, thrombotic microangiopathies and glomerulonephritis/ vasculitis. ATN is seen mostly in women with sepsis from any cause. Sepsis can lead to hypotension, decreased renal perfusion and ATN. Common causes of sepsis during pregnancy include pyelonephritis, pneumonia, chorioamnionitis and septic abortion. Due to physiologic hydronephrosis during pregnancy, asymptomatic bacteriuria in pregnancy can be complicated by ascending infection and pyelonephritis (Connolly and Thorp, 1999). Glomerular filtration rate is usually decreased in pregnant females with pyelonephritis without sepsis (Whalley *et al.*, 1975). Pyelonephritis is commonly caused by *Escherichia coli*, *Proteus mirabilis* and *Klebsiella*. Occasionally ATN is seen in conjunction with septic abortion especially in underdeveloped countries due to lack of sterile equipment. Bacteria responsible for septic shock following septic abortion include *E. coli*, group B streptococcus, anaerobic streptococci, *Bacteroides* species, *Clostridium* species and enterococci (Sweet and Gibbs, 2009). Cortical necrosis is caused by obstetric hemorrhage which can occur at any stage of pregnancy but common during last trimester.

Thrombotic microangiopathies include preeclampsia/HELLP, Acute Fatty Liver of Pregnancy (AFLP), Hemolytic Uremic Syndrome (HUS/TTP) and Systemic Lupus Erythematosus (SLE) with the antiphospholipid antibody syndrome. These conditions are characterized by presence of hemolytic anemia, low platelets, hypoglycemia, high lactate dehydrogenase level and disseminated intravascular coagulation. It is usually difficult to distinguish these conditions clinically but both laboratory and clinical parameters help in making likely diagnosis.

Obstructive nephropathy is very rare in pregnancy and can be caused by compression of ureters by gravid uterus (Courban *et al.*, 1997). This can occur frequently if pregnancy is multiple gestation pregnancy, polyhydramnios and pre-existing uterine fibroids. Maternal genitourinary anomalies or prior surgery can also predispose to obstructive uropathy, particularly in patients with unilateral kidney or collecting system (Fox *et al.*, 1978). Nephrolithiasis in pregnancy can also give rise to AKI as incidence of stones in pregnancy is the same as in non pregnant females of reproductive age (Butler *et al.*, 2000). These stones are

composed of calcium oxalate and calcium phosphate in majority of cases. Nephrolithiasis can predispose to infection of urinary tract and induce premature labor. Ultrasound is the best way to diagnose obstruction and stones. The management of urinary calculi during pregnancy is conservative with adequate hydration, analgesics and antibiotics if complicated by superimposed infection. Thiazide diuretics and allopurinol are usually contraindicated during pregnancy. 24 h urine studies are done after delivery of the baby to delineate the underlying metabolic propensity to stone formation. Most stones pass spontaneously, but in some cases ureteral catheterization and ureteral stents may be needed to relieve obstruction. Treatment of AKI during pregnancy is usually supportive with prompt restoration of hypovolemia in volume depleted conditions and emergent delivery of baby later in pregnancy due to severe preeclampsia or HELLP syndrome. No specific therapy is effective in acute cortical necrosis. Plasmapheresis may be indicated in cases with TTP. Patients with HELLP or AFLP require prompt delivery. Both hemodialysis and peritoneal dialysis can be used in pregnancy if indicated. Sepsis responds to treatment with antibiotics and volume resuscitation. Survival is dependent on management and recovery of AKI (Gammill and Eyabalan, 2005).

In some cases of AKI during pregnancy, renal biopsy may need to be performed to diagnose underlying cause of AKI. Renal biopsy is safe during pregnancy. However, morbidity of this procedure during pregnancy may be high. Usually renal biopsy is indicated in pregnancy in patients with proteinuria not due to preeclampsia and sudden deterioration of renal function before 32 weeks of gestation without any apparent cause because treatment of preeclampsia is delivery of the baby and placenta whereas proteinuria unrelated to preeclampsia requires drug therapy and not delivery of the baby. Complication risk of renal biopsy including bleeding is 1.6- 4.4% (Dennis *et al.*, 1968). The mortality rate from renal biopsy remains very low (Packham and Fairley, 1987). Procurement rate of tissue is high in pregnancy and in 80% of patients a specific glomerulonephritis may be diagnosed (Lindheimer and Davison, 1987). Renal biopsy is performed under ultrasound guidance and histology may help direct disease specific treatment in 66-100% of cases.

D-chronic kidney disease in pregnancy: Pregnant women with pre-existing chronic kidney disease are at increased risk for adverse maternal and fetal outcomes. They can have rapid deterioration of renal function during pregnancy and can develop preeclampsia (Sanders and Lucas, 2001). The fetus is usually low

birth weight, preterm delivery is common and perinatal mortality rate is high in patients with chronic kidney disease (Jones and Hayslett, 1996; Hou, 1999). The physiologic increase in renal blood flow and GFR expected during pregnancy is inadequate in patients with chronic kidney disease (Hou, 1999). The demand for increased renal blood flow during pregnancy may exacerbate renal damage in presence of chronic kidney disease. The degree of renal impairment affects maternal and fetal outcomes independent of the type of renal disease. Usually women with mild impairment of renal function (Cr 1.4 mg dL⁻¹ or less) and no proteinuria have better maternal and fetal outcomes than women with more severe renal impairment. Serum creatinine value greater than 2.0 mg dL⁻¹ carries 30% risk of accelerated loss of renal function during and after pregnancy. Pregnant women with serum creatinine >2.5 mg dL⁻¹ have 70% chance of preterm delivery and 40% risk of preeclampsia (Sanders and Lucas, 2001; Jones and Hayslett, 1996). Women with autosomal dominant polycystic kidney disease with normal renal function usually complete pregnancy successfully (Vora *et al.*, 2008). Patients with Systemic Lupus Erythematosus (SLE) and lupus nephritis can experience flare of lupus during pregnancy which can be associated with high risk of preterm delivery, spontaneous abortion and preeclampsia (Rahman *et al.*, 1998; Khamashta and Hughes, 1996). This risk is greatest in patients with SLE with history of lupus nephritis and it is associated with high risk of preeclampsia. Lupus flare can be differentiated from preeclampsia based on presence of hematuria and red blood cell casts in urine in lupus nephritis whereas urine sediment is bland in preeclampsia patients. Serum complement levels are low in patients with lupus flare and normal in preeclampsia. Occasionally renal biopsy may be indicated for diagnosis of lupus flare from preeclampsia due to differences in treatment options. Lupus patients should be in complete remission and should receive minimal immunosuppression before planning pregnancy (Moroni and Ponticelli, 2005). Diabetes Mellitus remains the commonest cause of chronic kidney disease throughout the world (USRDS 2004). More women with diabetes mellitus become pregnant these days (Dunne, 2005). Like pregnant patients with SLE, diabetic women with or without nephropathy are at increased risk of adverse fetal and maternal outcomes during pregnancy as compared to no diabetic pregnant females (Dunne *et al.*, 2003). This risk multiplies with presence of proteinuria and impaired renal function (Ekbohm, 1999). Poor glycemic control before and during pregnancy has been associated with preeclampsia and serious fetal outcomes. Endocrinology consult is recommended before pregnancy (Suhonen *et al.*, 2000). Pregnancy in diabetic woman with impaired renal function is associated with rapid decline in renal function especially in postpartum period.

Table 4: Acute Kidney Injury Network (AKIN) Criterion for Classification and Staging of Acute Kidney Injury (AKI)

Definition and Stages	Serum Creatinine	Urine Output
Increase in serum creatinine by 0.3mg/dl or >1.5times the baseline within 48 h		
Stage 1	Increase in serum creatinine by 0.3mg/dl or >1.5-2.0 times baseline	<0.5ml/kg/hour for more than 6 h
Stage 2	Increase in serum creatinine by >2.0 times baseline-<3 times baseline	<0.5ml/kg/hour for more than 12 h
Stage 3	Increase in serum creatinine >3.0 times baseline	<0.3ml/kg/hour for more than 24 h or anuria for more than 12 h

Aggressive blood pressure control before and after pregnancy may attenuate the postpartum decline in renal function (Rossing *et al.*, 2002). ACE inhibitors and angiotensin receptor blockers are contraindicated during pregnancy due to risk of fetal malformations (Podymow *et al.*, 2004). Therefore diabetic females with impaired renal function should be advised to postpone pregnancy until after kidney transplantation (Table 4).

E-Pregnancy in End Stage Renal Disease (ESRD):

Patients with End Stage Renal Disease receiving chronic dialysis have problems with conception due to dysfunction of hypothalamus-pituitary-gonadal system. This may be due to disruption of gonadotropin releasing hormone from hypothalamus (Leavey and Weitzel, 2002). The incidence of pregnancy in female patients with ESRD receiving dialysis is 1.5- 2.0% (Hou, 1994; Okundaye *et al.*, 1998). Usually 50% of these pregnant females give birth to live infants, most of which are premature.

Management of a pregnant dialysis patients includes aggressive control of blood pressure, longer dialysis sessions >20 h per week as it prolongs gestation and improves fetal outcome (Okundaye *et al.*, 1998; Hou, 2003). Frequent adjustment of dry weights to allow for weight gain expected during pregnancy and avoidance of hypovolemia. Medications should be carefully reviewed to avoid drug toxicity to the fetus such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Use of erythropoietin should be optimized to keep hemoglobin between 10-11gm/dl. Incidence of preeclampsia during pregnancy is difficult to determine due to inability to apply standard criterion used for non pregnant females. The nephrologist and obstetrician should work together closely for fetal well being. Pregnancy in women on peritoneal dialysis has similar outcome as patients on hemodialysis even though data is very limited (Jefferys *et al.*, 2008).

F-renal transplantation and pregnancy:

Renal transplantation can reverse infertility in patients on dialysis within six month. Transplantation induces restoration of hormonal imbalance back to normal in women of childbearing age group (Lessan-Pezeshki

et al., 2004). Women with renal transplantation should postpone pregnancy for two years after transplantation to avoid morbidity and mortality ERAEDTAG, 2002. The transplant recipients with normal renal function, small stable doses of immunosuppression and no prior rejection episodes can consider conception as early as 1 year post transplant (McKay and Josephson, 2006). Renal allograft function remains stable during pregnancy provided baseline graft function is normal and significant hypertension is not present ERAEDTAG, 2002.

The transplant recipient is at risk of various complications during pregnancy including infections which can be both bacterial and viral. The common infections seen are cytomegalovirus, herpes simplex and toxoplasmosis, bacterial urinary tract infections which can affect fetus. Hypertension is commonly encountered from use of calcineurin inhibitors for immunosuppression. Preeclampsia can complicate 25-30% of pregnancies in renal transplant recipients (Armenti *et al.*, 2006; Gutierrez *et al.*, 2005). One should monitor immunosuppressive drug therapy closely during pregnancy due to their effects on fetus, altered absorption and metabolism due to change in renal hemodynamics (Garcia-Donaire *et al.*, 2005). Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be discontinued in all pregnant women due to their effects on the fetus. Sirolimus is contraindicated during pregnancy due to teratogenicity (Danesi and Tacca, 2004). MMF is associated with developmental toxicity to the fetus, malformations and can be associated with spontaneous abortion (Ray *et al.*, 2004). Table 5 gives an overview of various immunosuppressive drugs in renal transplant recipients and their use during pregnancy.

Data on fetal outcome in renal transplant recipients is derived from various registries. 22% of pregnancies in transplant recipients end in first trimester due to combination of miscarriage or elective abortions (Armenti *et al.*, 2006). Those which continues on result in successful outcome in 90% of cases. There is usually risk of low birth weight or preterm delivery in these pregnancies (Armenti *et al.*, 2006; Gutierrez *et al.*, 2005). Vaginal delivery is safe and cesarean section in performed only for obstetrical indications in these patients.

Table 5: Immunosuppressive drugs in pregnancy

Drug	FDA category	Use in pregnancy	Precautions during pregnancy
Prednisone	B	Used safely in doses of 5-10mg/day and can be given in high doses at delivery time	Can cause fetal growth retardation
Cyclosporin	C	Can be used at low doses	Requires frequent monitoring of levels due to decreased GI absorption and metabolism. Can cause fetal growth retardation
Tacrolimus	C	Can be used at low doses although less data available	Frequent monitoring of the level required
Azathioprine	D	Safe at doses <2mg/kg/day	can be associated with fetal growth retardation at high doses
Sirolimus	C	Teratogenic in animals but no human studies on safety	Should be discontinued in pregnant transplant patients
Mycophenolate mofetil	D	Cannot be used in pregnancy due to teratogenicity in both animals and humans	Contraindicated for use in pregnancy
Antithymocyte globulin OKT3	C	No animal data on safety	No human data on safety
	C	Safety data limited documenting safety	Limited safety data confined to few case reports

Renal disorders in non pregnant females: Females can suffer from any renal disorder in non pregnant state which encompasses acute kidney injury in non pregnant condition due to various insults, chronic kidney disease due to systemic diseases or nephrotic syndrome due to various glomerular diseases. This section focuses on renal issues seen due to various gynecologic problems in females.

A-uterine fibroids: Uterine fibroids are the most common pelvic tumors in females (Baird *et al.*, 2003; Buttram and Reiter, 1981). They are benign monoclonal tumors arising from smooth muscles of the myometrium. These tumors can be intramural, sub mucosal, subserosal and cervical in location. They occur in females of reproductive age and present with various symptoms, e.g., abnormal uterine bleeding, pelvic pain or pressure or reproductive problems. Myomas are clinically apparent in approximately 12-25% of females of reproductive age (Downes *et al.*, 2010). Rarely, uterine fibroids can affect urinary tract and give rise to various renal problems. To date, Urinary Retention (UR), Acute Kidney Injury (AKI), Chronic Kidney Disease (CKD) and Hypertension have been reported due to uterine fibroids.

Urinary Retention (UR): Uterine myomas can cause compression of the urinary bladder and urethra due to mass effect. Urinary retention can be acute or chronic asymptomatic (Novi *et al.*, 2004; Kuroda *et al.*, 1999; Yang and Huang, 2002). This can occur both in non pregnant and pregnant conditions. In normal pregnancy, the uterus may partially obstruct the ureters at pelvic brim which results in dilatation of ureters without worsening renal function (2). In myomatous uterus, the uterus is irregularly shaped and can cause specific symptoms due to pressure from myomas at specific locations. Anteriorly situated fibroids can cause direct pressure on urinary bladder. A fibroid situated in

posterior part of the uterus can push the entire uterus forward and cause compression of the urinary bladder. Urinary retention due to fibroids results from displacement of the cervix superiorly and anteriorly in supine position. It causes compression of the lower part of urinary bladder leading to obstruction of the internal urethral meatus.

Acute Kidney Injury (AKI): AKI due to uterine fibroid occurs very rarely. It can be seen in both in pregnant and non pregnant women with pre-existing fibroids (Brandes and Fritsche, 1991; Elia *et al.*, 1982). AKI can occur due to obstruction of the urinary tract. Pregnancy results in growth of myoma under hormonal changes. Impaction of a retroverted gravid uterus can occur in pregnancy complicated by uterine fibroids which can result in formation of pelvic adhesions and contracted pelvis.

In nonpregnant females, urinary retention can result from various causes like urinary tract infection, medications, poor detrusor contractility. Fibroids cause mechanical compression of the bladder resulting in outflow obstruction and urinary retention. Diagnosis is made by urodynamic assessment and neurophysiological evaluation of the pudendal and sacral nerves. Treatment includes immediate relief of obstruction by catheterization. Ultimately, patients need myomectomy or hysterectomy or uterine artery embolization (UAE). UAE may cause immediate relief of symptoms of retention before any appreciable change in size of the myoma (Kagan and Mich, 2008). This could be due to relief of ischemia due to hypervascular fibroids on surrounding organs (Fig. 1).

Chronic kidney disease: Chronic Kidney Disease (CKD) due to uterine fibroid has been described in the literature (Bansal *et al.*, 2009). CKD from uterine fibroids results from chronic obstruction due to compression of urinary tract by the uterine fibroids. The site and degree of urinary tract obstruction

commonly depend on number and location of fibroids. Cervical fibroids are commonly associated with obstruction than fundal or central fibroids. Usually hysterectomy is indicated for symptomatic cure although it may not be the best choice in women who have not completed their family. Myomectomy and uterine artery embolization are other choices for therapy of uterine fibroids. Myomectomy is associated with high risk of bleeding and preceding uterine artery embolization may help to reduce size of the fibroids and make myomectomy easier.

Hypertension: Secondary Hypertension is another complication of myomas. It results from development of hydronephrosis caused by large myomas. It can occur in both pregnant and non pregnant females (Satin *et al.*, 1993) and is usually relieved by placement of nephrostomy tubes. Animal experiments have shown that Hypertension is related to degree of hydronephrosis, is salt sensitive and rennin levels are increased in hydronephrotic rats as compared to control group (Carlstrom *et al.*, 2006). Other studies have shown that ureteral obstruction can cause renal injury with subsequent fibrosis via oxidative stress and decreased Nitric oxide activity which leads to increased Tubuloglomerular Feedback (TGF) and hypertension. Other suggested mechanisms to hypertension include increased intra-renal pressure with compression of the intrarenal veins against renal capsule which leads to decreased GFR. This results in compensatory increased proximal tubular reabsorption of sodium and water causing increased plasma volume and hence hypertension.

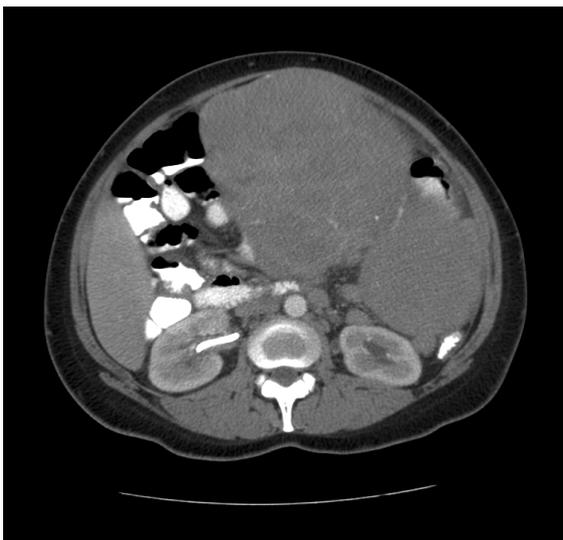


Fig. 1: This shows a large uterus with fibroids and right sided hydronephrosis

Malignancies of female reproductive system: Female reproductive system malignancies like uterine and cervical cancers can cause similar spectrum of renal problems in affected patients as caused by uterine fibroids.

CONCLUSION

Renal disorders related to female reproductive system are commonly encountered by nephrologists during practice especially during pregnancy. A detailed knowledge of these problems help manage these patients better and reduce complication rate.

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