

Pregnancy Associated Kidney Diseases

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Abstract: Significant physiologic mechanisms that alter systemic and renal hemodynamics play an important role in the renal response to changes in fluid and electrolytes during normal pregnancy. Acute kidney Injury (AKI) in pregnancy remains a cause of significant fetomaternal mortality and morbidity. AKI develops most often due to hyperemesis gravidarum or septic abortion (in the first trimester). Hypertensive complications of pregnancy (preeclampsia/eclampsia or hemolysis, elevated liver enzymes, and low platelets count syndrome (HELLP)) are the leading cause of AKI in pregnancy worldwide. Chronic Kidney Diseases (CKD); Stages, fetal &maternal complications and recommendation with Pregnancy. Although pregnancy after renal replacement therapy is feasible, complications are relatively common and this needs to be considered in patient counseling and clinical decision making.

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Renal hemodynamics and physiologic changes in normal pregnancy:

Maternal accommodation to normal pregnancy begins shortly after conception with significant hemodynamic and urinary tract alterations noted as early as 6 weeks gestation. Maternal systemic vascular resistance falls significantly, leading to a decrease in mean arterial pressure that reaches a nadir between 18 and 24 weeks gestation^{1, 2}. Kidney size increases by about 1cm in length during pregnancy and may persist for up to 12 weeks postpartum secondary to; increase in renal vascular volume and increased capacity of dilated urinary collecting system (physiologic hydronephrosis of pregnancy) due to estrogen and progesterone. Mechanical obstruction of ureters in pregnancy (right > left, may be due to dextrorotation of uterus by sigmoid colon and resolves within 48 hours post partum in 50% of cases³.

Glomerular hyperfiltration:

Glomerular hyperfiltration is the most notable physiologic adaptation to normal pregnancy, due to increase in GFR and renal plasma flow (RPF) which clinically presents as a decrease in the serum creatinine⁴. Relaxin and nitric oxide (NO) have been implicated as key factors in mediating the renal vasodilatation and glomerular hyperfiltration that is characteristic of normal pregnancy⁴. Circulating blood volume increases by 50% (plasma more than red blood cells, causing physiologic anemia of pregnancy) and cumulative sodium retention (500 to 900 mEq) stimulated by decreased peripheral

vascular resistance due to, resistance to angiotensin II secondary to high prosatacyclin and prolactin levels, leading to increase extracellular fluid volume, weight gain and “benign” edema of lower extremities³.

Electrolyte Balance:

Total body sodium increases on an average by 3-4 mEq/d, ultimately producing net balance of 900-1000 mEq, and total body potassium also increases by up to 320 mEq by the end of gestation⁵. This retention of sodium is a complex interplay of natriuretic and ant natriuretic factors (Table 1), namely GFR, atrial natriuretic peptide, and progesterone for sodium wasting as well as aldosterone deoxycorticosterone for sodium conservation⁶.

Tubular Function:

Due to increase in GFR and RPF, increased urinary excretion of glucose, amino acids, uric acid and water-soluble vitamins occurs. Most obstetric guidelines define significant protein excretion as 300 mg in a 24-hour period⁴.

Pregnancy associated acute kidney injury (P-AKI)

AKI in pregnancy (P-AKI) remains a cause of significant fetal (39%) and maternal (20%) mortality and morbidity⁷. Its definition varies from mild increase in serum creatinine 0.8 mg/dl to dialysis requirement. However, serum creatinine level decreases during normal pregnancy and it reaches levels around 0.6–0.7 mg/dl during the third trimester⁸. Serum uric acid and proteinuria or new

currently evaluated (neutrophil gelatinase associated lipocalin) biologic markers may help predicting the occurrence of AKI in pregnant women⁹. The incidence of P-AKI has decreased in the last decades

mainly because of the near disappearance of postpartum sepsis after the legalization of abortion and the improved management of hypertensive complication with pregnancy⁷.

Table 1: Major changes in electrolytes (Na and K) during pregnancy⁶.

Physiologic changes	Effect during pregnancy	changes during pregnancy
GFR	Natriuretic	Increase in early pregnancy until labor
atrial natriuretic peptide	Natriuretic	Increase at 12WK till 36 WK
Progesteron	Natriuretic/Anti Natriuretic	Increase after ovulation ; peak at 4 WK before delivery
Aldesteron	Anti Natriuretic / Natriuretic	Increase at 6 WK until labor
Deoxycortison	Anti Natriuretic	Increase in 1 st trimester peak in third 3 rd trimester
Na-K TRANSPORTER	Anti Natriuretic	Increase during pregnancy

In early pregnancy, prerenal azotemia is only secondary to hyperemesis gravidarum or hemorrhage of spontaneous abortion¹⁰. Acute tubular necrosis may be due to volume depletion secondary to hyperemesis gravidarum or hemorrhage of spontaneous abortion. Septic abortion with associated shock in the first trimester, gram-negative sepsis, most commonly *Escherichia coli*, with resultant hypotension and Myoglobulinuria secondary to Clostridium-induced myonecrosis of uterus. It diagnosed by Clinical setting, urinalysis with coarse granular casts, and increased fractional excretion of sodium. Supportive therapy with intravenous fluid, antibiotics, and dialysis as indicated³.

Renal cortical necrosis is more frequently seen in older women, multigravidas, and multiple gestations, and is caused by obstetric catastrophes (abruptio placentae, septic abortion, severe pre-eclampsia and amniotic fluid embolism. Primary disseminated intravascular coagulation and severe renal ischemia may be initiating event in this disorder. It presents with gross hematuria, flank pain, and severe oliguria or anuria. It diagnosed noninvasively by computed tomography demonstrating a radiolucent rim in the cortex parallel capsule, or invasively by renal biopsy or angiogram with patchy blood flow or absent nephrogram¹¹. Renal functional recovery typically requires months, it may be incomplete, and may lead to end-stage renal disease.

Bacteriuria and urinary tract infections (UTI):

Asymptomatic bacteriuria is risk factor for UTI in pregnancy and bacteremia, septic shock renal failure, or mid trimester abortions. Asymptomatic bacteriuria can be treated with 3-day course of amoxicillin, a cephalosporin, or nitrofurantoin. UTI frequency is same as in nonpregnant women. Risk factors include diabetes, sickle cell trait or disease, as well as lower socioeconomic status. Contributing

factors are dilated urinary collecting system combined with slowed emptying, urine stasis, and vesicoureteral reflux. Glucosuria and aminoaciduria also help bacterial growth. UTI can evolve into pyelonephritis in about one third of cases. Pyelonephritis can be treated with intravenous cefazolin or ceftriaxone, although ampicillin in combination with gentamicin can be used. Trimethoprim-sulfamethoxazole, tetracycline, and fluoroquinolones should be avoided³.

Acute kidney injury in Late Pregnancy

P-AKI occurs mainly during the late third trimester and around delivery, due to hypertensive complications of pregnancy (pre-eclampsia (PE), eclampsia, hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome) and pregnancy-related TMA.

Pre-eclampsia (PE):

PE is defined by as the new onset of hypertension (BP>140/90) and proteinuria >300 mg protein in a 24-h urine collection) after 20 wk of gestation. PE occurs mainly during the late second and third trimester, but it may occur up to the time of delivery and even postpartum⁷. PE/E accounts for 15%-20% of P-AKI cases¹². Risk Factors for PE are Primigravida, diabetes, Preexisting hypertension, renal disease, twin gestation, hydatidiform mole, fetal hydrops family history¹³.

Pathology and pathogenesis:

The characteristic pathologic changes with preeclampsia include swelling of the endothelial cells (glomerular endotheliosis), ballooning of capillary loops into the tubule, fibrinogen and lipid in the lumens. These changes resolve 2-4 weeks postpartum. The pathogenesis of PE related to altered vascular endothelial growth factor (VEGF) signaling, which is now recognized as crucial to podocyte

health and normal barrier function¹². Also increasing expression of soluble fms like tyrosine kinase-1 (sFlt1) and decreased expression of placental growth factor (PlGF). sFlt1, a circulating alternative splice variant of the VEGF receptor Flt1, binds and functionally inactivates both VEGF and PlGF¹⁴. sFlt1 via functional VEGF deficiency, results in vasoconstriction, endothelial dysfunction in resistance size small arteries Placental hypoxia, uteroplacental hypoperfusion, over expression of angiotensin II (AngII) type 1 receptor autoantibodies (AT R-AA), immune deregulations (complement and natural killer cells) and increased release of oxidative stress products in the placenta^{14, 15}. Some researches study key roles for deficiencies of (atrial natriuretic peptide converting enzyme) and of atrial natriuretic peptide in the defective trophoblast invasion and remodeling of uterine spiral arteries that accompany many cases of PE¹⁶. PE also characterized with increasing endothelin and thromboxane that predisposes to platelet aggregation, intravascular clotting and decreased synthesis of the vasodilators (prostacyclin and nitric oxide)^{3, 17}.

Clinically: PE usually begins after 20 weeks of pregnancy it manifested by De novo hypertension new onset proteinuria and sever PE manifested by PE with one or more of the following; Systolic BP <160 mm Hg or diastolic BP <110 mm Hg on two occasions at least 6 hr apart while on bed rest, Proteinuria >5 g in a 24-hr urine specimen or dipstick proteinuria <3+ on two random urine samples at least 4 hr apart, Oliguria (<500 mL urine output over 24 hr), visual disturbances, Severe headache, mental status changes, Hepatocellular injury (transaminase elevation) to at least twofold over normal level, Thrombocytopenia (<100,000), growth restriction, Fetal Cerebrovascular accident and pulmonary edema or cyanosis^{7, 17}.

PREVENTION of PE: Aspirin, in Low-dosage to oppose the prominent alterations in prostacyclin-thromboxane balance, **calcium supplementation**, **Antioxidant** as vitamin C and E supplementation due to major role for oxidative stress, **Vit D**, **folic acid** and **L-arginine**, NO donors, as the role NO in the pathogenesis of PE, L-arginine, might be effective for the prevention endothelial protective effect of VEGF and PlGF^{18, 19, and 20}.

HELLP syndrome:

Many investigators consider the syndrome to be variant of PE. It occurs typically in the third trimester, but may be diagnosed in the second trimester or postpartum period. 20% of women with severe PE develop HELLP syndrome. Acute renal failure occurs in 3%-15% of women with HELLP syndrome²¹.

Pathogenesis: It occurs due to involve alterations in platelet activation, increases in proinflammatory cytokines, and segmental vasospasm with vascular endothelial damage. An association with a defect in long-chain hydroxyacyl-coenzyme A dehydrogenase (LCHAD) has also been described so, overlap of HELLP syndrome, acute fatty liver of pregnancy and DIC may be present⁷.

Clinical Presentation: 90% of patients present with generalized malaise, 65 % with epigastric pain, 30 % with nausea and vomiting, and 31% with headache.

The physical examination may be normal in patients with HELLP syndrome. Mostly 90% right upper quadrant tenderness, Edema is not a useful marker and Hypertension and proteinuria may be absent or mild^{1, 22}.

Diagnosis: Hemolysis: Abnormal peripheral smear (spherocytes, schistocytes, and burr cells), total bilirubin level > 1.2 mg/dL (1,22), Lactate dehydrogenase level > 600 U/L, elevated liver function test (Serum aspartate amino transferase level > 70 U/L) and Low platelet count (< 150 000/mm³)¹.

Acute fatty liver of pregnancy (AFLP):

AFLP is a sudden catastrophic illness of acute liver failure with coagulopathy that affects women in the third trimester of pregnancy. It is estimated to affect between 1/7000 and 1/20,000 pregnancies²³ with high maternal (12.5%) and fetal mortality rates as high as 85%²⁵.

Pathology and pathogenesis: The disease results from an autosomal recessive genetic error that causes a defect on LCHAD, an enzyme involved in mitochondrial fatty acid beta-oxidation. Heterozygous mothers are usually asymptomatic until pregnant with a homozygous fetus; there is an excessive fetal fatty acid accumulation to be released into the maternal circulation. The increased load of long-chain fatty acids is deposited in liver tissue and leads to impaired hepatic function in the mother^{24, 25}. Genetic screening for the LCHAD mutations in neonates born to mothers with AFLP or severe HELLP syndrome is recommended, as early diagnosis and treatment of the neonate with dietary modification can be life-saving²⁶.

The histopathologic diagnosis of AFLP is based on the presence of lipid microvesicle infiltration of the hepatocytes, without inflammation or necrosis²⁶.

Clinical manifestations: The usual symptoms in the mother are prodromal phase: non specific including nausea, vomiting, anorexia and abdominal pain moderate isolated transaminitis to fulminant hepatic failure: Jaundice and fever may occur in 70% of Patients. This may progress to fulminant hepatic

failure: involvement of additional systems, including acute renal failure, hepatic encephalopathy and pancreatitis^{24,25}. **Diagnosis:** Include hyperbilirubinemia, increased transaminases, hypoglycemia and leukocytosis. Evidence of coagulopathy is a key feature with hypofibrinogenemia, prolonged prothrombin time, depressed antithrombin III levels, and thrombocytopenia. Hypoalbuminemia may occur. Rising uric acid levels and impaired renal function may also be seen²⁶. Abdominal ultrasound may show fat deposition in the liver but, as the hallmark of this condition is microvesicular steatosis this may not be seen on ultrasound. Rarely, the condition can be complicated by rupture or necrosis of the liver, which may be identified by ultrasound²⁷.

AKI treatment in pregnancy:

There are 3 aspects to consider in the management of AKI related to pregnancy, renal function supportive measures, dialysis and treatment of the underlying disease¹³.

Renal function supportive measures: include general measures as avoiding nephrotoxic drugs, treatment of infectious disease and intravenous fluids to maintain renal perfusion. These general measures are followed by pharmacologic therapy of AKI and its known complications: hypertension, hyperkalemia, metabolic acidosis and anemia²⁸. The first-line treatment options in pregnancy are methyldopa, labetalol, the dihydropyridine calcium channel blockers and Hydralazine is more commonly used in severe hypertension. Some of the antihypertensive drugs are contraindicated in pregnancy (such as angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists) or are not recommended (such as diuretics because of the high risk for volume depletion)^{26,29}.

Hyperkalemia: The administration of insulin, glucose and ion exchange resin are recommended for treatment. Metabolic acidosis is corrected with sodium bicarbonate¹³. Anemia: associated with AKI, blood transfusion is recommended in a cute therapy. The erythropoiesis-stimulating agents are safe in pregnancy³⁰. Dialysis is indicated for uremic symptoms (encephalopathy, pericarditis or neuropathy), volume over load, hyperkalemia and/or metabolic acidosis unresponsive to initial medical treatment. However, authors recommend starting dialysis earlier, when GFR falls to below 20 ml/min per 1.73 m²³¹. Treatment of the underlying disease

The treatment of severe preeclampsia/HELLP syndrome depends on illness severity, gestational age and fetal well-being. Before 24 weeks of gestation, pregnancy discontinuance is recommended since studies show no fetal survival benefit and only increase the risk of severe maternal complication²².

Between 24 and 32 weeks of gestation, the expect-ant management is a reasonable approach. Delivery is the treatment of choice for pregnancies ≥ 32 weeks²⁴. Parenteral magnesium is the cornerstone of our therapy to prevent or treat eclampsia²³. Some studies show the benefit of corticosteroid therapy for the prognosis of HELLP syndrome²⁵. Case reports have described successful treatment of AFLP with molecular adsorbent recirculating systems (MARS), a High-flux hemofiltration system that removes albumin bound toxins from the blood²⁶ also Plasma exchange in the postpartum setting has also been described in AFLP^{25,26,30}.

Pregnancy and chronic kidney diseases (CKD):

CKD affects 3% of women aged 20_39 years³¹. Frequently CKD may be diagnosed during pregnancy; however, where possible, pre-pregnancy counseling for women with CKD affords the opportunity to adjust medication, optimize hypertension control, stabilize renal function and educate the woman about possible adverse events which may arise during or as a consequence of her pregnancy³². Systematic review has suggested that women with CKD have at least at twofold higher risk of developing adverse fetal outcomes compared with without CKD, and that adverse maternal events were more fivefold higher³³.

Pregnancy complications: maternal and fetal according to stages: CKD stages 1 and 2:

They are defined by estimated GFR > 60 ml/min per 1.73 m²) plus urine abnormalities or structural kidney abnormalities, with serum creatinine 100 μ mol/L. Usually Pregnancy with early CKD generally does not precipitate either a worsening or an accelerated worsening of maternal kidney function^{34,35}. Although the risk of preeclampsia (10%-20%) remains greater than that for pregnant women without CKD (5%)³⁶. Recently successful fetal outcomes have been reported to be as high as 98 % however; rates preterm delivery (11%) and low birth weight (5%-26%) continue to be higher than in healthy controls^{37,38}.

CKD stages 3 and 4: CKD stages 3 and 4 are defined as e GFR < 60 ml/min per 1.73 m² and e GFR < 30 ml/min per 1.73 m². There is a reduction in fertility and fetal loss is greater³⁹. Preeclampsia may occur in up to 40%-60% with CKD stage 3 or 4, which may be early and severe. Prematurity is common (39%-64%) and despite major advances in neonatal care, very preterm infants frequently have sensory impairment and intellectual disability³⁴. Important predictors of permanent deterioration of renal disease in women with Pre-pregnancy of GFR

of less than 40 ml/min per 1.73 m² and proteinuria exceeding 1 g/24 hours⁴⁰.

Pregnancy and Renal replacement Therapy Pregnancy with haemodialysis (HD):

Stage 5 CKD is defined as e GFR <15 ml/min per 1.73 m² or being on dialysis. Advances in therapy have resulted in 40% of women under the age of 55. Many women on dialysis are oligomenorrhic or amenorrhic, but up to 1 in 200 women of child bearing age on dialysis become pregnant⁴². Fetal survival rates for pregnant women on haemodialysis have also increased to 87%, with an average gestational age of 32.7 + or - 3 weeks⁴³. Subsequently, predialysis education and counseling sessions should include the conception rates, contraception options, pregnancy complications, statistics of a live baby and all additional haemodialysis requirements and tests involved in caring for a pregnant woman being able to now continue to menstruate⁴¹.

Diagnosis: Ultrasound is the best form of detecting an accurate gestational age, as the patient may be anuric. A pregnancy test diagnosis is usually not made till 16.5 gestational weeks as "amenorrhic and nausea often mask the presence of pregnancy"⁴¹.

Complications: fetal distress and preterm delivery (usually before 32 weeks gestation)⁴⁴. Polyhydramnios is a common complication and found in 30-70% of pregnant women on HD. It occurs in response to the high placental BUN concentration and fetal diuresis, therefore treated by haemodialysis³⁷, increasing the amount of haemodialysis^{43,45}. Haemodialysis Time should be at least 20 hours per week⁴⁶. AS it leads to less uremic environment for the fetus and decreased incidence of polyhydramnios, more liberal diet (potassium and protein) and intake of fluid for the mother and More control of the mothers BP and a decreased need for antihypertensive^{45,47,48}. **Hypertension:** 80% of pregnant dialysis patients have some degree of hypertension (>140/90) and 40% have severe hypertension with a systolic >200mmHg or diastolic >110mmHg. Methyl dopa, B-blockers and hydralazine are the main antihypertensive medications used on pregnant women and in severe hypertension clonidine and calcium channel blockers are recommended. With note that Magnesium and Nifedipine should not be used together as it can cause severe hypotension⁴⁵.

Ideal Body Weight (IBW): Approximately 12-16kg of weight gain should be expected during pregnancy with approx 0.3-0.5 kg per week in the 2nd and 3rd trimesters^{41,45}. Anemia Pregnant women require a 50-100% higher dose Erythropoietin hormone (EPO), increase iron to 200mg iron intravenously weekly in order to maintain transferrin

saturation > 25 % and folate⁴⁹. **Diet** Zinc, vitamins, Vitamin D, phosphorus and calcium (should be guided by measurement of levels of vitamin D, parathyroid hormone, calcium and phosphorus)⁴⁵ are required and minimum daily intake of protein per day should be 1.8/kg/day⁴⁷. Blood Weekly blood results are recommended Targets as are follows keep blood urea <15mmol/L, Pre dialysis creatinine level of 4.5mg/dL and Maintain pH > 7.2⁴⁸. Dialysate: phosphate may need to be added to the dialysate the sodium on the machine should be decreased from 140 to 135. This will also help control the pregnant woman's BP therefore. Heparin is safe to use unless there is vaginal bleeding, as it doesn't cross the placenta⁴¹. For labor, The pregnant woman should be positioned semi reclined or on a bed with a left lateral tilt from 20 weeks, to ensure decompression of vena cava⁴⁹. The risk of preterm birth is 70 -100%. Delivery is recommended between 34-36 weeks and no later than 38 weeks. Causes of premature delivery include "polyhydramnios, maternal hypertension and premature rupture of the membranes"⁴⁵.

Pregnancy with peritoneal dialysis (PD):

The number of pregnant individuals on PD is approximately 2 to 3 times lower than that of those on HD due to the hypertonic peritoneal milieu and volume of fluid in abdominal cavity having adverse effects on the ovum or its transport and peritonitis resulting in adhesions and failure of implantation (50). Babies born to mothers on PD have higher birth weights compared with those on HD there is less preeclampsia but premature labor and peritonitis are more common⁵¹. The majority of women who conceive while on PD are often changed to HD due to perceived issues of volume, inadequate clearance and less experience⁵².

Pregnancy with renal transplantation: With the recovery of renal function following renal transplantation, both fertility and libido are restored. Approximately 74% of pregnancies in kidney transplant recipients end successfully in live births⁵³. The outcomes of pregnancy depend on pre-pregnancy renal function. If a woman has a pre pregnancy serum creatinine level of less than 1.4 mg dl, a successful pregnancy is 96 %. However, creatinine is more than 1.4 mg/dl, a successful pregnancy drops to 70-75 percent and one third of these pregnancies end in therapeutic or spontaneous abortions⁵⁴. Potential causes of worsening renal function in a pregnant transplant patient include preeclampsia, acute or chronic rejection recurrent kidney disease, dehydration, and obstruction of the transplant ureter by the pregnant uterus, infection and medication toxicity. Unfortunately, women with excellent graft function and "normal" GFR still have

an increased risk of preeclampsia, potentially due to previous endothelial injury or undetectable graft fibrosis⁵⁵. The overall post-transplant live birth rate was 74% and the overall post-transplant miscarriage was 14.0% compared to 66.7% and 17.1% respectively for the general US population. However, complications of preeclampsia (27.0%), gestational diabetes (8.0 %) cesarean section (56.9%) and preterm delivery (45.6%) were higher than the general US population (3.8%, 3.9% and 12.5%, respectively)⁵⁶. Management: All women of child-bearing age should be counseled regarding the possibility, timing and risks of pregnancy after kidney transplantation^{55, 57}. In the past the recommendation was waiting to two years after successful transplantation before conception. But the American Society of Transplantation Consensus Conference Report states that now, patients may become pregnant at any time as long as graft function is optimal(defined as a serum creatinine <1.5 mg dl, urinary protein excretion <500 mg/day and no concurrent infection) even, about 6-12 months after receiving renal transplant⁵⁸. Immunosuppressive dosing is stable at maintenance levels⁵⁹.The immune compromised increases risk of maternal-fetal transmission of infections and its potential risk to the mother as well as the fetus also needs to be considered⁵⁵. Women with renal transplants should be reassured that they can have normal vaginal deliveries and that the allograft will not be damaged by pregnancy or delivery due to its anatomical position, although cesarean section continues to be the most common delivery mode in these women⁵⁵.

The US Food and Drug Administration (FDA) classification for commonly used immunosuppressive medication (55)

Corticosteroids: class B, No evidence of risk in humans. Prednisolone does not appear to have teratogenic activity in humans at therapeutic doses .In utero exposure of human fetuses to a high dose (>40 mg/day) increased the rate of spontaneous abortion, intrauterine fetal death, perinatal mortality, IUGR and LBW.

Administration of glucocorticoid throughout pregnancy may cause adrenal suppression but this is rare with doses < 15 mg/day. Thymic hypoplasia without a significant immune deficiency, depressed hematopoiesis, lymphopenia, hyponatremia and hyperkalemia have also Prednisolone been related to in utero exposure.

Cyclosporine: class C, Risks cannot be ruled out. It is associated with an increased Incidence of abortions, stillbirths, IUGR. Prematurity and LBW. Severe B cell depletion was described in newborns from renal transplant recipients receiving cyclosporine, azathioprine and Prednisolone, and this

depletion persisted at three months of life. Despite of known nephrotoxicity, infants antenatally exposed to cyclosporine had normal renal functions. A few isolated cases of minor abnormalities have been described including osseous hypoplasia (leg and foot).

Tacrolimus: class C, Risks cannot be ruled out. Preterm birth is common. Transient hyperkalemia and transient renal impairment are common. Cases of congenital malformation have been reported without any consistent pattern of affected organs.

Azathioprine: class D, Positive evidence of risk. The major reported side effects are spontaneous abortions, prematurity, IUGR and LBW. Infants from mothers administered azathioprine during pregnancy often presented neonatal leucopenia, thrombocytopenia, thymic hypoplasia, and decreased serum IgG, IgM, and or IgA levels. These immunological abnormalities were transient and usually resolved at 1 year of age.

Mycophenolate Mofetil: class D, Positive evidence of risk. It is contraindicated in pregnancy It is associated with high incidence of structural malformations, including hypoplastic nails and shortened fifth fingers, microtia and cleft lip and palate.

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