REVIEW ARTICLE

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

WILEY

Acute kidney injury during pregnancy in kidney transplant recipients

Anju Yadav[1] | **Maria Aurora Posadas Salas[2]** | **Lisa Coscia[3]** | **Arpita Basu[4]** |
Ana Paula Rossi[5] | **Deirdre Sawinski[6]** | **Silvi Shah[7]**

[1]Division of Nephrology, Department of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[2]Division of Nephrology and Hypertension, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

[3]Transplant Pregnancy Registry International, Gift of Life Institute, Philadelphia, Pennsylvania, USA

[4]Division of Transplant and Division of Nephrology and Hypertension, Emory University, Atlanta, Georgia, USA

[5]Piedmont Transplant Institute, Atlanta, Georgia, USA

[6]Division of Nephrology and Transplantation, Weill Cornell College of Medicine, New York, New York, USA

[7]Division of Nephrology, Department of Medicine, University of Cincinnati, Cincinnati, Ohio, USA

Correspondence
Silvi Shah, Division of Nephrology, University of Cincinnati, 231 Albert Sabin Way, MSB 6112, Cincinnati, OH 45267, USA.
Email: shah2sv@ucmail.uc.edu

Abstract

Pregnancy-related acute kidney injury (AKI) is a public health problem and remains an important cause of maternal and fetal morbidity and mortality. The incidence of pregnancy-related AKI has increased in developed countries due to increase in maternal age and higher detection rates. Pregnancy in women with kidney transplants is associated with higher adverse outcomes like preeclampsia, preterm births, and allograft dysfunction, but limited data exists on causes and outcomes of pregnancy-related AKI in the kidney transplant population. Diagnosis of AKI during pregnancy remains challenging in kidney transplant recipients due to lack of diagnostic criteria. Management of pregnancy-related AKI in the kidney transplant population requires a multidisciplinary team consisting of transplant nephrologists, high-risk obstetricians, and neonatologists. In this review, we discuss pregnancy-related AKI in women with kidney transplants, etiologies, pregnancy outcomes, and management strategies.

KEYWORDS
acute kidney injury, kidney transplant, pregnancy

1 | INTRODUCTION

The first successful pregnancy in a woman with kidney transplant occurred in 1958. Subsequent pregnancies in women with kidney transplants established that pregnancies were possible with successful maternal and fetal outcomes.[1] There is impairment of fertility in women with chronic kidney disease.[1] However, regular menstrual and ovulatory cycle may resume as early as 3 weeks after kidney transplantation, and the hypothalamic-pituitary-gonadal axis is restored to normal by 6 months after kidney transplantation.[2,3] KDIGO guidelines recommend delaying pregnancy until at least the first year post-transplant

to facilitate stabilization of kidney function for the best outcome.[4] But posttransplant pregnancy is not a "zero risk" choice given the potential for fetal, maternal, and allograft complications affecting outcomes.[5]

While preeclampsia, allograft rejection, preterm births, and stillbirths are all recognized as potential complications of pregnancy in women with kidney transplants, acute kidney injury (AKI) is rarely addressed in the literature. Hence, there is no definite data about the incidence of AKI in pregnant kidney transplant recipients. The incidence of pregnancy-related AKI has increased almost three-fold in developed countries due to advanced maternal age with increased comorbidities, lifestyle diseases like hypertension, diabetes and

obesity, and higher detection rates. Significant variability exists in the definition and diagnosis of pregnancy-related AKI in the kidney transplant recipients and in the general population.[6,7] Limited data exist on various etiologies and outcomes of AKI during pregnancy in women with kidney transplants which creates a significant knowledge gap.

2 | EFFECTS OF PREGNANCY ON KIDNEY ALLOGRAFT FUNCTION

In a normal pregnancy, glomerular filtration rate (GFR) increases by about 40%–60% due to hyperfiltration, vasodilation, and an increase in effective plasma flow which increases clearance of blood urea nitrogen and creatinine. During pregnancy, serum concentration of creatinine usually decreases below .8 mg/dl and blood urea nitrogen decreases below 12 mg/dl. Glomerular hyperfiltration also results in physiologic proteinuria of pregnancy.[8–10] The kidney allograft adapts to these physiological changes of pregnancy. There is an increase in creatinine clearance by about 30% in the first trimester, a slight decrease in creatinine clearance in the second trimester, and a return of serum creatinine to pre-pregnancy level by the third trimester.[11] The absence of a decrease in serum creatinine in early pregnancy portends a poor prognosis and clinicians should consider careful evaluation of kidney transplant recipients whose creatinine does not decrease with expected physiologic changes of pregnancy. It has been demonstrated that among women with chronic kidney disease stages 3–5, a gestational fall in serum creatinine of <10% of the pre-pregnancy creatinine (as well as chronic hypertension, and proteinuria) were associated with adverse pregnancy and kidney outcomes (preterm delivery, low birthweight and loss of maternal kidney function).[12] Additionally, an increase in the GFR causes physiological proteinuria of pregnancy, and women with kidney transplants have a higher 24-hour urine protein excretion as compared to healthy women.[13] Protein excretion in pregnant kidney transplant recipients may increase up to threefold by the third trimester, exceeding 500 mg as compared to 200 mg in healthy pregnant women and returns to baseline levels by 3 months postpartum.[11,14,15] An abnormal increase in proteinuria from baseline during pregnancy in women with kidney transplant should trigger an evaluation for various causes of AKI including preeclampsia and urinary tract infection.

3 | DIAGNOSTIC CRITERIA FOR PREGNANCY-RELATED ACUTE KIDNEY INJURY

There is a lack of consensus on the definition of pregnancy-related AKI in kidney transplant recipients. Traditionally, an acute rise in creatinine by greater than .5 mg/dl from the baseline within 48 h has been proposed as the defining criteria for pregnancy-related AKI. RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria proposed in 2004, AKIN (Acute Kidney Injury Network) criteria proposed in 2007, the KDIGO (Kidney Disease Improving Outcomes) guidelines that take into account the rise of creatinine over baseline or fall in eGFR, both as a percentage, and decrease in the urine output, are used to diagnose AKI in the general population, but have not been validated to diagnose pregnancy-related AKI in the kidney transplant population.[16–18] Due to physiological changes during pregnancy, the level of serum creatinine with a normal allograft function is lower than baseline, and ranges between .4 and .6 mg/dl range during the first trimester.[19] The physiological lowering of baseline creatinine in pregnancy along with non-validation of the diagnostic criteria makes the detection of AKI in pregnancy in kidney transplant recipients challenging.[6] This results in delay in diagnosis of AKI during pregnancy in women with kidney transplants. Consequently, the incidence of AKI in pregnant kidney transplant recipients remains unclear.[20]

Serum creatinine remains the most utilized, easily accessible, and affordable biomarker to diagnose AKI in the kidney transplant population. Biomarkers such as cystatin c are not routinely used to diagnose AKI in clinical practice yet. Other injury markers like neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury marker-1 (KIM-1) have not been validated in this population. Hematuria and proteinuria may be used as surrogates for AKI along with serum creatinine, and/or changes in urine output. If kidney function is not assessed regularly, subtle increases in serum creatinine can be missed easily, resulting in delayed detection of potential significant degree of kidney injury. Hence, assessment of proteinuria and hematuria should be part of routine assessment in pregnant kidney transplant recipients. These can be the early indicators of AKI due to graft dysfunction, acute rejection, and recurrent or de novo glomerulonephritis. Different etiologies for AKI can be classified according to different stages of pregnancy,[18] although there might be a significant overlap during each trimester (Table 1).

4 | CAUSES OF PREGNANCY-RELATED ACUTE KIDNEY INJURY IN THE KIDNEY TRANSPLANT RECIPIENTS

Table 2 shows the causes of pregnancy-related AKI in the kidney transplant population classified by prerenal, renal, and postrenal etiologies. Most of these pregnancy-related AKI etiologies overlap with the general population, while some are specific to the kidney transplant population.[6,18,21]

During the second and third trimesters, the causes of AKI are more specific to an isolated pregnancy-related complication in the kidney transplant population. These include preeclampsia, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, acute fatty liver of pregnancy, thrombotic microangiopathies like thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome, renal vein thrombosis, and urinary tract infection. Immunologic changes during pregnancy with fluctuating levels of immunosuppressive medications can lead to the development of de novo donor-specific antibody post-pregnancy leading to antibody mediated rejection.[22] However, the actual incidence of de novo donor-specific antibody in kidney transplant recipients during pregnancy is unknown and needs future investigation. Timely diagnosis and management of these can

TABLE 1 Differential diagnosis for pregnancy-related AKI in kidney transplant recipients based on pregnancy trimester

Pregnancy trimester	Differential diagnosis
First trimester	Hyperemesis gravidarum Septic abortion/early miscarriages Medication-related
Second trimester	Preeclampsia/eclampsia Pyelonephritis HELLP syndrome Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome Recurrent glomerulonephritis (membranous nephropathy, lupus nephritis)
Third trimester	HELLP syndrome Thrombotic thrombocytopenic purpura/atypical hemolytic uremic syndrome Preeclampsia/eclampsia Recurrent glomerulonephritis (membranous nephropathy, lupus nephritis) Obstructive uropathy Placental abruption Placental hemorrhage Acute fatty liver of pregnancy
Peripartum	Bleeding with an atonic uterus Uterine rupture Obstetrical trauma
Postpartum	Atypical hemolytic uremic syndrome Nonsteroidal anti-inflammatory drug use Puerperal sepsis Recurrent glomerulonephritis like lupus nephritis Postpartum cardiomyopathy

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelets.

help prevent the progression of CKD in transplant allograft as well as improve maternal and fetal outcomes. Mild physiological hydronephrosis is a common finding in both pregnant patients and kidney transplant recipients. The degree of hydronephrosis more than expected (moderate/severe or worsening) should, therefore, prompt a workup for AKI due to postrenal etiology. Obstructive AKI in pregnant kidney transplant recipients may occur in the second and third trimester due to the gravid uterus pressing on the kidney. Recipients with ureteral strictures requiring stents are at risk of developing obstructive uropathy as well.[19,23] Abdominal compartment syndrome may infrequently be seen in multifetal gestation and multiorgan transplant recipient.[21] Important causes of pregnancy-related AKI in the kidney transplant populations are explained below in detail.

Hyperemesis gravidarum: Hyperemesis gravidarum usually occurs in the first trimester of pregnancy where women usually present with severe persistent nausea, vomiting, and poor oral intake that can lead to AKI due to volume depletion. Other clinical manifestations of hyperemesis gravidarum include weight loss >5% of pre-pregnancy weight, hypokalemia, and metabolic alkalosis. In severe cases, ketonuria, mild elevation of aminotransferases, and mild hyperthyroidism may occur.[6,18,21]

Preeclampsia: Preeclampsia usually occurs in the second or third trimester. Patients can present with a myriad of symptoms such as abdominal pain, nausea, vomiting, headaches, visual disturbances, or worsening pedal edema. Preeclampsia is diagnosed by new onset of hypertension after 20 weeks of gestation defined by blood pressure ≥140/90 mm Hg on two occasions 4 h apart, or ≥160/110 mm Hg

within a shorter interval, and proteinuria ≥ 300-mg/24-h urine or spot urine protein creatinine ratio .3 (dipstick 1+). Preeclampsia can be diagnosed in the absence of proteinuria if any of the following signs of end organ dysfunction are present including elevated serum creatinine >1.1 mg/dl or doubling of serum creatinine in the absence of other kidney disease, thrombocytopenia (<100,000 ml), elevated liver transaminases ≥2 times normal, pulmonary edema or, cerebral/visual symptoms. There are several biomarkers that have been investigated in patients with chronic kidney disease and kidney transplant patients to differentiate pre-eclampsia from physiologic changes in pregnancy, but they have not been validated and are not widely available. In patients with history of hypertension or proteinuric kidney disease, diagnosis of preeclampsia is therefore challenging and eventually makes management difficult.[8,24]

Hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome: Diagnosis of HELLP syndrome is made by (a) presence of microangiopathic hemolytic anemia as evidenced by schistocytes in blood smear, lactate dehydrogenase >6000 U/L, low haptoglobin, or elevated total bilirubin ≥1.2 mg/dl; (b) elevated liver transaminases and in particular, aspartate transaminase >70 UL; and (c) low platelet count <100 × 10⁹/L.[6,18,21]

Acute fatty liver of pregnancy: Acute fatty liver of pregnancy is an extremely rare condition which usually occurs in the third trimester characterized by acute onset liver failure with coagulopathy and can progress to fulminant liver failure leading to encephalopathy. Diagnosis is made by elevated liver enzymes and bilirubin, low fibrinogen, prolonged prothrombin time, decreased antithrombin III

TABLE 2 Pregnancy-related acute kidney injury classified by prerenal, renal, and postrenal etiologies in the kidney transplant population

Pre-renal	Hyperemesis gravidarum
	Heart failure
	Hemorrhage
	Liver dysfunction
	Calcineurin inhibitor toxicity
	Diarrheal infections
	Sepsis
	Ectopic pregnancy
	Bleeding
	Ovarian hyperstimulation syndrome
Renal	Immunologic: acute cellular rejection, acute antibody-mediated rejection, combined rejection, or newly diagnosed or progressive transplant glomerulopathy
	Recurrent disease: C3 glomerulopathy, thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome, IgA nephropathy, recurrent or de-novo glomerulopathy, such as focal segmental glomerulosclerosis, membranous nephropathy, pauci-immune glomerulonephritis, lupus nephritis, anti-phospholipid antibody syndrome, disseminated intravascular coagulation, progression of chronic kidney disease
	Medication-induced: calcineurin inhibitor, intravenous contrast dye exposure, antibiotics, antivirals
	Infection-related: polyomavirus nephropathy, cytomegalovirus systemic infection, pyelonephritis, chorioamnionitis, sepsis
	Tubulointerstitial disease: acute tubular necrosis, acute interstitial nephritis, acute cortical necrosis
	Pregnancy-related complications: acute fatty liver of pregnancy, preeclampsia, HELLP syndrome, amniotic fluid embolus
	Malignancy: post-transplant lymphoproliferative disease or any other malignancy (infiltrative or obstructive)
	Vascular: renal artery thrombosis, renal vein thrombosis, kidney allograft thrombosis, thrombotic microangiopathy
Post-renal	Hydronephrosis due to uterine compression
	Ureteral obstruction due to stones, tumor, or bladder outlet obstruction
	Neurogenic bladder
	Polyhydramnios
	Large uterine fibroids
	Injury to ureters or bladder during cesarean section
	Abdominal compartment syndrome in the setting of multiple gestation or multi-organ transplants

Abbreviation: HELLP, Hemolysis, Elevated Liver enzymes, and Low Platelets.

and platelets, hypoglycemia, and leukocytosis. Clinical manifestations include fatigue, nausea, vomiting, abdominal discomfort, jaundice, and fever. Acute fatty liver of pregnancy is a diagnosis of exclusion.[6,18,21]

Thrombotic microangiopathy including thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome: Thrombotic microangiopathies are characterized by evidence of microangiopathic hemolytic anemia (high lactate dehydrogenase, low haptoglobin, and schistocytes on peripheral smear), low platelet counts (<150000/mcl or 50% from baseline), and evidence of systemic manifestations. Thrombotic thrombocytopenic purpura can affect any trimester of pregnancy and involves the neurological system more commonly than atypical hemolytic uremic syndrome. Diagnosis of thrombotic thrombocytopenic purpura is made by serological testing demonstrating ADAMTS13 activity <10%. Atypical hemolytic uremic syndrome typically occurs in the first 6 months postpartum and has a greater likelihood of kidney involvement compared to thrombotic thrombocytopenic purpura. Genetic tests for alternate complement pathway mutations are available to make a diagnosis of atypical hemolytic uremic syndrome but are limited by cost and time to report. Physiological increases in complement related proteins in normal pregnancy should be considered when interpreting complementation levels

and should be correlated clinically. Appropriate management should not be delayed.[6,18,21]

Acute cortical necrosis: Acute cortical necrosis can occur any time during pregnancy and hence, a high index of suspicion is necessary. Causes of acute cortical necrosis includes septic abortion early in pregnancy (<20 weeks' gestation), peripartum complication such as placental abruption, sepsis, amniotic fluid embolization, or retained product of conception. Clinical history and evaluation with kidney ultrasound or computed tomography scan are required to make the diagnosis when AKI is present. Imaging studies will show hypoechoic or hyperdense areas in the kidney cortex.[25]

Infections: Opportunistic infections, bacteremia from septic abortion, or systemic sepsis can cause AKI in the pregnant kidney transplant recipients. Polyomavirus infection (BK nephropathy) and cytomegalovirus viremia can present as AKI. Patients with prior history of these infections or with high-risk cytomegalovirus serostatus should prompt regular monitoring of kidney function. Urine analysis, urine culture, blood culture, and specific serologies should be done when suspected based on history and clinical presentation.[6,18,21]

Acute pyelonephritis: Gestational pyelonephritis is a serious condition associated with premature labor, intrauterine growth

restriction, sepsis, and AKI. Kidney transplant recipients are inherently at a higher risk for urinary tract infections and hence higher risk for AKI from pyelonephritis, especially with a gravid uterus and increased urinary reflux. Clinical manifestations include fever, chills, nausea, vomiting, flank pain, and costovertebral angle tenderness. Laboratory assessment will reveal peripheral leukocytosis, and urinalysis showing pyuria and bacteriuria with/without hematuria, and white blood cell casts. The computed tomography scan may show normal kidney morphology, swelling in affected areas of the kidney, nonspecific perinephric fat stranding, or perinephric abscess. In patients who have history of recurrent urinary tract infections, prophylactic antibiotics should be considered during pregnancy.[6,18,21]

Acute rejection: Pregnancy is a state of immunological tolerance associated with decreased immune activity of lymphocytes which creates tolerance to the fetus and may benefit the kidney allograft. However, there is a possibility that the antigenic stimulus provided by the fetus may trigger graft rejection as well. Pregnancy in kidney transplant recipients poses a risk for acute rejection not only because of alterations in a previously stable immunosuppressive regimen but also due to the risk of sensitization. Human leukocyte antigen (HLA) allosensitization may occur during pregnancy but might not be detected since HLA antibodies are not routinely monitored during pregnancy. In the absence of risk factors, acute rejection rates are similar to the general transplant population, about 9.0% during pregnancy and 1.3% postpartum.[3] Acute cellular or antibody-mediated rejection can cause AKI in pregnancy. Rates of graft loss at 2 years postdelivery in pregnant kidney transplant recipients vary from 5% to 9%.[26–28] Woman' baseline calculated panel reactive antibody level or development of de-novo donor-specific antibodies, changes in dose of immunosuppression, poor medication adherence, or effect of pregnancy on immunosuppressive medication pharmacokinetics can predispose to acute rejection. Kidney biopsy is the gold standard for diagnosis of rejection. The availability of noninvasive biomarkers (genomic or donor derived cell-free DNA techniques) might be useful in kidney transplant recipients with advanced pregnancy or high risk for biopsy complications from a hematological perspective, however, these have not been studied in pregnant kidney transplant recipients. Third-generation genomics might be more useful compared to the cell-free DNA technique. Details about biopsy during pregnancy are outlined later in this article.

Medications: Calcineurin inhibitors remain the standard of care immunosuppression among kidney transplant recipients. Fluctuating levels of calcineurin inhibitors in pregnant kidney transplant recipients puts them at higher risk of AKI especially with nephrotoxic effect. Pharmacokinetic changes happen in pregnancy and calcineurin inhibitor levels need to be monitored at least monthly. There are many limitations in interpreting tacrolimus levels in pregnancy as outlined by Herbert et al.[29] Tacrolimus is measured in whole blood and due to the anemia and hypoalbuminemia in pregnancy, whole blood levels may decrease without a significant decrease in unbound tacrolimus, which is the relevant "free" level. Unfortunately, free tacrolimus levels are not available outside of research settings. We recommend to target slightly lower tacrolimus level during pregnancy with close monitoring of albumin and hemoglobin that may further guide adjusting the

dose. Therefore, even a normal appearing tacrolimus level may cause calcineurin inhibitor associated nephrotoxicity. Very high calcineurin inhibitor trough levels can lead to AKI by vasoconstriction of the afferent and efferent glomerular arterioles causing reduced renal blood flow. Proteinuria from the mammalian target of rapamycin (mTOR) inhibitors can be exacerbated resulting in AKI. Antibiotics, antivirals, or antifungals can be nephrotoxic in a dose-dependent manner. Safety in pregnancy should be checked for these agents and dosed based on kidney function in pregnant patients.

5 | RISK FACTORS FOR PREGNANCY-RELATED AKI IN KIDNEY TRANSPLANT RECIPIENTS

Table 3 elucidates the risk factors for pregnancy-related AKI in kidney transplant recipients. Certain factors make kidney transplant recipients more susceptible to AKI during pregnancy. In addition to usual etiologies for AKI in pregnancy, certain causes of AKI are specific for pregnant kidney transplant recipients, including immunological injury (acute cellular rejection or acute antibody-mediated rejection), recurrent glomerulonephritis, immunosuppressive medications (calcineurin inhibitors or mTOR inhibitors), urinary tract obstruction, hematologic or malignancy-related causes, all in the setting of a solitary kidney transplant.

6 | DIAGNOSTIC TESTING FOR AKI DURING PREGNANCY IN KIDNEY TRANSPLANT RECIPIENTS

Follow-up should be intensified in kidney transplant recipients to assist with early identification of AKI and treatment of complications, including acute rejection, hypertension, anemia, coagulation disorders, and timely planning of delivery.[5] The recommendations by Italian best practice guidelines[5] is to have at least one nephrology follow-up with blood and urinary tests every 2–4 weeks in pregnant kidney transplant recipients with stable renal function, controlled blood pressure and no proteinuria. More frequent follow up is recommended if risk factors are present. Urinalysis should be monitored for evidence of hematuria and proteinuria. Renal function and electrolytes must be monitored with a routine chemistry panel. A frequent fetal ultrasound might be necessary to ensure stability and viability. Pregnancies in women with kidney transplants should be treated as high risk even if with seemingly normal parameters.

Diagnostic testing for assessment of AKI in pregnant kidney transplant recipients is listed in Table 4.

There is no consensus regarding appropriate timing for kidney biopsy in pregnant kidney transplant recipients. With advanced technology, kidney transplant biopsies are being done more routinely and can provide an important and prompt diagnosis.[30] The limited literature regarding kidney biopsy in pregnancy indicates 7% versus 1% risk of bleeding in pregnancy versus postpartum period.[31] Postpregnancy transplant biopsies demonstrated an increase in vascular injury as compared to pre-pregnancy biopsies, after adjusting for time, which could

TABLE 3 Risk factors for pregnancy-related AKI in kidney transplant recipients

- Solitary kidney
- Susceptibility to volume depletion due to autoregulation impairment
- Immunological risk factors
- Increased risk of abdominal compartment syndrome depending on the number of transplants or multiorgan transplants, etiology of end-stage kidney disease such as polycystic disease or multiple gestations.
- Long term exposure to medications such as calcineurin inhibitors that cause acute vasoconstriction and nephrotoxicity
- Increase of urinary reflux during pregnancy in addition to inherent risk with transplant ureter
- Increased risk of acute urinary retention and ureteral strictures
- Exposure to nephrotoxic antimicrobials and immunoglobulins
- Increased risk of viral infections such as polyomavirus nephropathy and cytomegalovirus
- Possible recurrences of glomerulonephritis, atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and antiphospholipid syndrome
- Hematological causes such as antiphospholipid syndrome, hypercoagulable state, and renal vein thrombosis
- Vascular causes such as renal artery stenosis
- Increased likelihood for post-transplant lymphoproliferative disorder and requiring nephrotoxic chemotherapy agents

TABLE 4 Diagnostic testing for pregnancy-related AKI in kidney transplant recipients

1. Urinalysis with microscopy

1. Quantify protein excretion with random urine protein to creatinine ratio

1. Complete blood count with differential and peripheral smear if microangiopathic hemolytic anemia is suspected

1. Renal and liver function panel including coagulation panel

1. Direct and indirect bilirubin, lactate dehydrogenase

1. ADAMTS-13 and the genetic test for alternate complement pathways if clinically indicated

1. Allograft kidney ultrasound

1. Kidney allograft biopsy (based on pregnancy trimester)

1. Urine and blood culture (if indicated)

1. Monitoring for donor specific antibody

1. BK, herpes simplex virus, and cytomegalovirus polymerase chain reaction

1. Autoimmune panel if recurrent glomerulonephritis is suspected (antinuclear antibody, M-type phospholipase A2 receptor antibody, complement)

be related to high incidence of preeclampsia in this population.[32] A multidisciplinary approach should be employed to decide if a biopsy is necessary.

7 | MANAGEMENT OF AKI DURING PREGNANCY IN KIDNEY TRANSPLANT RECIPIENTS

Management of pregnancy-related AKI in kidney transplant recipients is complex as pregnant kidney transplant recipients may have several comorbidities and are usually on multiple medications. Management of pregnancy-related AKI involves a multidisciplinary team approach consisting of transplant nephrologists, maternal-fetal medicine specialists, transplant surgeons, and neonatologists. Home and clinic blood pressures should be monitored closely, especially in the second and third trimester. Any indication of hypertension with or without proteinuria

should prompt more frequent clinic visits and any signs of preeclampsia should prompt hospital admission and monitoring with fetal doppler.

General measures to treat pregnancy-related AKI in kidney transplant recipients include prompt identification and reversal of the underlying cause of kidney injury. For prerenal AKI, intravenous fluids should be administered promptly. Care must be taken in patients with heart failure, eclampsia, or endotoxin-mediated injury. For ischemic AKI due to anemia, a blood transfusion may be necessary to maintain tissue and fetal oxygenation. On the other hand, if the recipient is suffering from hypervolemia, they may be given loop diuretics. Diuretics are usually safe is pregnancy but due to their potential risk of volume depletion or precipitating pre-eclampsia, discussion between all care team members is important. Serum electrolytes must be monitored closely and corrected with appropriate supplementation or binders. Nutritional support is also an important part of the care of the pregnant kidney transplant recipients with AKI. Symptomatic

or asymptomatic urinary tract infection and pyuria should be treated in pregnant women for 3 weeks with broad spectrum antibiotics initially and then narrowed down to specific antibiotics based on susceptibility studies. Pregnant kidney transplant recipients with primary herpes infection can transmit the infection to the fetus during vaginal delivery. Hence, cesarean section should be considered in these patients. Reducing the overall immunosuppression level along with antivirals for treatment of cytomegalovirus and herpes simplex virus infection on are usually the standard of practice and often warranted in cases presenting with AKI in the setting of opportunistic infections. In conditions such as thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome; plasmapheresis, eculizumab, and rituximab might be indicated. There is data available on safety of eculizumab during pregnancy. Safety data on use of monoclonal antibodies during pregnancy should be discussed and risk-benefit discussions should be held between physicians and patients. Small studies have demonstrated B-cell depletion in <10% of neonates but no long-term assessment of the safety of rituximab in neonates is available.[33] Treatment of glomerulonephritis includes steroids and immunosuppressive therapy; the risks and benefits should be considered when therapy is initiated in a pregnant woman.[8] Azathioprine and calcineurin inhibitors (cyclosporine and tacrolimus) are not teratogenic and are commonly used immunosuppressive drugs in pregnancy. During pregnancy, higher doses of tacrolimus and cyclosporine are needed to achieve therapeutic targets, and therefore frequent monitoring of drug trough levels is warranted.[11] Treatment for rejection is dependent on biopsy findings (antibody-mediated rejection vs. acute cellular rejection), presence or absence of donor specific antibody, and history of infections. High-dose steroids have been successful in treating allograft rejection during pregnancy and remain the first-line treatment. Escalating immunosuppression by titrating the dose of calcineurin inhibitors or use of B cell depleting monoclonal antibodies can be used after thorough discussion with the patient. If despite efforts to reverse AKI, patient's kidney function continues to deteriorate, then kidney replacement therapy must be initiated when indicated. Consideration must be given to the prompt and safe delivery of the fetus.

8 | OUTCOMES WITH PREGNANCY-RELATED AKI IN THE KIDNEY TRANSPLANT POPULATION

Most studies pertain to only pregnancy outcomes in the kidney transplant population. Predictors of good maternal and fetal outcomes include younger maternal age, stable graft function with no recent episodes of graft rejection, serum creatinine level of <1.5 mg/dl, proteinuria of <500 mg/day, and normal or well-controlled hypertension.[26,28,34–37] Although AKI in pregnancy is associated with high maternal and fetal morbidity and mortality in the general population, data on maternal and fetal outcomes in pregnant kidney transplant recipients who develop AKI is scarce. Pregnancy in kidney transplant recipients is associated with higher risks of hypertension, preeclampsia, preterm birth, low birth weight, and cesarean section.[26–28] However, the risk of birth defects is comparable with the

general population (4.5% vs. 3%–5%).[27] A recent meta-analysis of pregnancy outcomes suggested that the live birth rate among kidney transplant recipients may be higher than in the general population, 72.9% versus 62%, respectively.[28] Chewcharat et al. evaluated the outcomes of nearly 5.5 million pregnant women from 2009 to 2014 with no known kidney disease and compared it to 405 women with CKD stages 3–5 and 295 women with functioning kidney transplants. About 28% of pregnant women with CKD stages 3–5 and 5% of pregnant women with kidney transplants developed AKI during the hospitalization for delivery, versus only .1% of pregnant women with no known kidney disease. The study showed that pregnant kidney transplant recipients compared with pregnant women with no known kidney disease had about 11-fold higher odds of developing AKI during the delivery hospitalization (OR 10.46, 95% CI 5.33–20.56, $p < .001$).[38] A study in Norway examining pregnant kidney transplant recipients showed that women with preeclampsia had statistically significantly higher serum creatinine levels than women without preeclampsia when assessed during the first trimester of pregnancy, at delivery, and during the postpartum period, but no difference was seen in serum creatinine levels before pregnancy. In women with preeclampsia, there was four times higher risk of an increase greater than 20% in serum creatinine and eleven times higher risk of an increase greater than 50% in serum creatinine between the first trimester and postpartum. Episodes of acute rejection, however, were not recorded during any of the pregnancies.[39] Based on a large 15-year study of deliveries in Canada, the incidence of pregnancy-related AKI requiring dialysis was low (cumulative incidence of 1 per 10000). AKI requiring dialysis was nearly four times more likely in women with a major medical complication during pregnancy such as preeclampsia, thrombotic microangiopathy, pregnancy-related liver disease, sepsis, and postpartum hemorrhage. The mortality rate of women with AKI requiring dialysis was 4.3%, compared to .01% in women without kidney injury. Of women who survived, 3.9% remained dependent on chronic dialysis after 90 days postpartum.[40]

Bachmann et al. reported that despite a higher rate of preterm birth and low birth weight in pregnant kidney transplant recipients, child development up to age 2 years was appropriate.[41] General health and physical constitution of children were unremarkable with normal development in 94% at 12 and 24 months of corrected age, respectively. Malformations are not higher in babies of kidney transplant recipients if teratogenic drugs are avoided. In women with transplants, the risk of adverse maternal-fetal outcomes has been reported to be higher in multiple pregnancies as well as pregnancies from assisted fertilization.[5] The kidney allograft does not affect normal vaginal delivery and a cesarean section is not routinely indicated unless indicated for obstetric indications. In the event of surgery, care should be taken to avoid injury to the ureter of the kidney allograft, which may be anterior to the uterine artery. In the study by Bachman et al., 24 out of 32 (75%) pregnancies had a cesarean section in pregnant kidney transplant recipients. Of the 24 cesarean sections performed, 16 were due to maternal conditions, 5 due to fetal conditions (fetal distress during labor and fetal growth retardation), and 3 due to combined indications (one placental abruption and two placental insufficiency).[41] Five had pre-eclampsia and one of those patients developed aortic

dissection due to worsening hypertension, necessitating emergent cesarean section at 30 weeks of gestation. No kidney allograft injuries were reported in this study.

In the study of pregnant kidney transplant recipients[41] about half of patients reported >10 ml/min decline in kidney function at delivery compared to pre-pregnancy values (did not specify AKI incidence). At 6 months postpartum, median glomerular filtration (GFR) was 48 ml/min/1.73m2 (IQR 37, 60 ml/min/1.73 m^2). One year after delivery and at last follow-up, median GFR remained lower compared to pre-pregnancy levels at 50 ml/min/1.73 m^2. GFR at 24 months after delivery was lower than all other GFR values at delivery. Median proteinuria at delivery was 335 mg/g creatinine. All in all, 2-year graft survival after delivery was 92.8%. Overall, GFR at 2 years postpartum was still worse than at the date of delivery with the lowest values observed at 6 months postpartum. Extrapolating data from the general population, AKI leads to CKD progression or worsening interstitial fibrosis and tubular atrophy.

9 | CONCLUSION

Despite reports of successful pregnancy in solid organ transplant recipients, women with kidney transplants remain at higher risk for both maternal and fetal complications. Kidney transplant recipients are vulnerable to developing AKI during pregnancy for multiple reasons. Recognizing the risk factors that predispose this high-risk population to common prerenal, intrinsic, and postrenal insults of AKI is instrumental for timely diagnosis and management. Given the medical complexity of the pregnant kidney transplant recipient, a multidisciplinary team approach including the nephrologist, obstetrician, and neonatologist is crucial to ensure good outcomes. Robust multicenter studies investigating AKI in pregnant Kidney transplant recipients, incidence, diagnostic criteria, and establishing management guidelines are much needed.

CONFLICT OF INTEREST
None.

DATA AVAILABILITY STATEMENT
There is no data statement.

DISCLOSURES
This manuscript is a work product of the American Society of Transplantation's Women's Health Community of Practice

ORCID

Maria Aurora Posadas Salas https://orcid.org/0000-0001-7411-7154

Arpita Basu https://orcid.org/0000-0002-0533-4582

Silvi Shah https://orcid.org/0000-0002-9941-9404

REFERENCES

1. Murray JE, Reid DE, Harrison JH, Merrill JP. Successful pregnancies after human renal transplantation. *N Engl J Med*. 1963;269:341-343.
2. SahaMT S, Niskanen LK, Salmela KT, Pasternack AI. Time course of serum prolactin and sex hormones following successful renal transplantation. *Nephron*. 2002;92(92):735-737.
3. Gonzalez Suarez ML, Parker AS, Cheungpasitporn W. Pregnancy in kidney transplant recipients. *Adv Chronic Kidney Dis*. 2020;27(6):486-498.
4. Recipient KgT: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2009-Transplant-Recipient-Guideline-English.pdf 2009.
5. Cabiddu G, Spotti D, Gernone G, et al. A best-practice position statement on pregnancy after kidney transplantation: focusing on the unsolved questions. The Kidney and Pregnancy Study Group of the Italian Society of Nephrology. *J Nephrol*. 2018;31(5):665-681.
6. Taber-Hight E, Shah S. Acute kidney injury in pregnancy. *Adv Chronic Kidney Dis*. 2020;27(6):455-460.
7. Shah S, Meganathan K, Christianson AL, Harrison K, Leonard AC, Thakar CV. Pregnancy-related acute kidney injury in the united states: clinical outcomes and health care utilization. *Am J Nephrol*. 2020;51(3):216-226.
8. Gonzalez Suarez ML, Kattah A, Grande JP, Garovic V. Renal disorders in pregnancy: core curriculum 2019. *Am J Kidney Dis*. 2019;73(1):119-130.
9. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Adv Chronic Kidney Dis*. 2013;20(3):209-214.
10. First MR, Combs CA, Weiskittel P, Miodovnik M. Lack of effect of pregnancy on renal allograft survival or function. *Transplantation*. 1995;59(4):472-476.
11. Shah S, Verma P. Overview of pregnancy in renal transplant patients. *Int J Nephrol*. 2016;2016:4539342.
12. Wiles K, Webster P, Seed PT, et al. The impact of chronic kidney disease stages 3-5 on pregnancy outcomes. *Nephrol Dial Transplant*. 2020;36(11):2008-2017.
13. Kattah A, Milic N, White W, Garovic V. Spot urine protein measurements in normotensive pregnancies, pregnancies with isolated proteinuria and preeclampsia. *Am J Physiol Regul Integr Comp Physiol*. 2017;313(4):R418-r424.
14. Davison JM. The effect of pregnancy on kidney function in renal allograft recipients. *Kidney Int*. 1985;27(1):74-79.
15. Crowe AV, Rustom R, Gradden C, et al. Pregnancy does not adversely affect renal transplant function. *QJM*. 1999;92(11):631-635.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212.
17. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
18. Vinturache A, Popoola J, Watt-Coote I. The changing landscape of acute kidney injury in pregnancy from an obstetrics perspective. *J Clin Med*. 2019;8(9).
19. Vijayan M, Avendano M, Chinchilla KA, Jim B. Acute kidney injury in pregnancy. *Curr Opin Crit Care*. 2019;25(6):580-590.
20. de Buhren H, Hertig A. Staging pregnancy-related acute kidney injury according to kidney disease: improving global outcomes guidelines: what are the barriers?. *Nephrol Dial Transplant*. 2021;36(6):959-961.

21. Michalska M, Wen K, Pauly RP. Acute kidney injury in pregnant patient with pancreas-kidney transplant caused by abdominal compartment syndrome: a case presentation, review of literature, and proposal of diagnostic approach. *Can J Kidney Health Dis.* 2019;6:2054358119861942.

22. Sagasaki M, Nakada Y, Yamamoto I, et al. Antibody-mediated rejection due to anti-HLA-DQ antibody after pregnancy and delivery in a female kidney transplant recipient. *Nephrology (Carlton, Vic).* 2018;23 Suppl 2:81-84.

23. Rao S, Jim B. Acute kidney injury in pregnancy: the changing landscape for the 21st century. *Kidney Int Rep.* 2018;3(2):247-257.

24. Shah S, Gupta A. Hypertensive disorders of pregnancy. *Cardiol Clin.* 2019;37(3):345-354.

25. Gupta A, Kuperman M, Shah S. N-methylamphetamine ("Crystal Meth")-associated acute renal cortical necrosis. *Kidney Int Rep.* 2018;3(6):1473-1476.

26. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant.* 2011;11(11):2388-2404.

27. Moritz MJCS, Coscia LA, Kliniewski D, McGrory CH, Armenti DP, Carlin FR, Transplant Pregnancy Registry International 2017 Annual Report, Gift of Life Institute, 2018. 2018.

28. Shah S, Venkatesan RL, Gupta A, et al. Pregnancy outcomes in women with kidney transplant: metaanalysis and systematic review. *BMC Nephrology.* 2019;20(1):24.

29. Hebert MF, Zheng S, Hays K, et al. Interpreting tacrolimus concentrations during pregnancy and postpartum. *Transplantation.* 2013;95(7):908-915.

30. Dines V, D'Costa M, Fidler M, Kattah A. The role of kidney biopsy in diagnosis of preeclampsia in kidney transplant patients. *Hypertens Pregnancy.* 2020;39(4):418-422.

31. Piccoli GB, Daidola G, Attini R, et al. Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. *BJOG.* 2013;120(4):412-427.

32. Kattah AG, Albadri S, Alexander MP, et al. Impact of pregnancy on GFR decline and kidney histology in kidney transplant recipients. *Kidney Int Rep.* 2022;7(1):28-35.

33. Fakhouri F, Vercel C, Fremeaux-Bacchi V. Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. *Clin J Am Soc Nephrol.* 2012;7(12):2100-2106.

34. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplantat.* 2009;9 Suppl 3:S1-S155.

35. McKay DB, Josephson MA. Pregnancy after kidney transplantation. *Clin J Am Soc Nephrol.* 2008;3 Suppl 2(Suppl):S117-S125.

36. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int.* 2010;77(4):299-311.

37. Assalino M, Podetta M, Demuylder-Mischler S, et al. Successful pregnancy and delivery after simultaneous islet-kidney transplantation. *Am J Transplant.* 2018;18(8):2075-2078.

38. Chewcharat A, Kattah AG, Thongprayoon C, et al. Comparison of hospitalization outcomes for delivery and resource utilization between pregnant women with kidney transplants and chronic kidney disease in the United States. *Nephrology (Carlton, Vic).* 2021;26(11):879-889.

39. Majak GB, Reisæter AV, Zucknick M, et al. Preeclampsia in kidney transplanted women; Outcomes and a simple prognostic risk score system. *PLoS One.* 2017;12(3):e0173420.

40. Hildebrand AM, Liu K, Shariff SZ, et al. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. *J Am Soc Nephrol.* 2015;26(12):3085-3091.

41. Bachmann F, Budde K, Gerland M, et al. Pregnancy following kidney transplantation – impact on mother and graft function and focus on childrens' longitudinal development. *BMC Pregnancy Childbirth.* 2019;19(1):376.