

Management of Acute Kidney Injury in Pregnancy for the Obstetrician



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KEYWORDS

- Acute kidney injury • Pregnancy-related acute kidney injury
- Atypical hemolytic uremic syndrome • Thrombotic microangiopathy • Preeclampsia
- Hypertensive disorders of pregnancy

KEY POINTS

- The physiologic changes in the kidney pose a challenge to the diagnosis of acute kidney injury in pregnancy.
- Assessment of baseline renal function and proteinuria early in prenatal care is essential for accurate diagnosis of pregnancy-related acute kidney injury.
- Identification of women at risk for acute kidney injury plays a crucial role in prompt diagnosis and prevention of acute kidney injury.
- Optimal management of women with pregnancy-related acute kidney injury requires a multidisciplinary team approach.
- It is prudent to limit renal biopsy to women with a suspicion of any condition that is severe enough to warrant urgent treatment or a change in management.
- The indications for starting renal replacement therapy in pregnancy-related acute kidney injury are the same as those in the nonpregnant population.

BACKGROUND

The incidence of pregnancy-related acute kidney injury (PR-AKI) varies widely across the world, with reported incidence of 1 in 20,000 pregnancies¹ to as much as 1 in 50 pregnancies.² Many factors contribute to this variation in incidence, such as lack of uniform defining criteria, physiologic changes in pregnancy that affect interpretation of laboratory tests, and regional differences in factors contributing to acute kidney injury (AKI). In addition, AKI (a term that has replaced acute renal failure) is often under-recognized until it is severe. Often there is a lack of information on baseline

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prepregnancy serum creatinine (SCr) values in this population, which further poses a problem. The diagnostic accuracy of the currently accepted definition of AKI in the general population is not fully known in pregnancy and perhaps is inadequate.

Some nations report a bimodal distribution with an early peak of AKI as a consequence of septic abortions and a second peak later in pregnancy from hypertensive disorders of pregnancy, along with obstetric complications such as hemorrhage. Although the etiology of PR-AKI varies based on the country of origin, in most regions, including low-income countries, preeclampsia and eclampsia account for 5% to 20% of cases, with one study reporting 36% of PR-AKI to be from hypertensive disorders of pregnancy (**Box 1**).² The risk of PR-AKI is higher in the setting of early-onset (<32 weeks gestation) preeclampsia. Other major causes of PR-AKI in developing countries include sepsis and severe hemorrhage, whereas primary renal disease, thrombotic microangiopathy (TMA), and acute fatty liver of pregnancy (AFLP) are more common in the developed nations. Pregnancy may also unmask underlying primary renal disease or modify the course of preexisting renal disease.

Although overall a decrease in the incidence of PR-AKI has been reported, a substantial increase in AKI during pregnancy has been reported recently in the United States and Canada, with a higher increase reported in the United States. PR-AKI was also associated with a higher mortality rate, ranging from 17.4% of deaths during delivery hospitalization to 31.5% of deaths among postpartum hospitalizations in those with AKI.^{3,4} This change could be attributed to several reasons such as, an increase in testing for the condition and lowering of the threshold for diagnosis, with the older literature relying a higher decline in glomerular filtration rate (GFR) to diagnose AKI.^{5,6} A potential diagnostic ascertainment bias is further supported with an increased need for renal replacement therapy (RRT) seen among pregnant women with chronic kidney disease (CKD) and chronic hypertension who develop AKI.⁴ Although risk factors such as diabetes, preeclampsia, and chronic hypertension predisposing women to PR-AKI have increased, the recent study by Mehrabadi⁴ found that these factors contributed little to the increase in overall acute renal failure.

Although most women with AKI in pregnancy recover renal function, up to a third do not fully recover and can have serious long-term outcomes.^{2,7,8} Some may require RRT, and, when this option is unavailable (as in many parts of the world), it may result in mortality. Maternal and fetal outcomes, thus, depend on optimal management of AKI.

Following a brief overview of physiology, this article provides an in-depth review of management of the spectrum of AKI occurring in pregnancy. Significant anatomic and physiologic changes occur in the kidneys during pregnancy and some of these changes begin soon after conception. Specific attention is given to current research and the newer therapeutic options.

Anatomic changes in pregnancy

The length of the kidney increases by 1 to 1.5 cm.

The volume of the kidney increases up to 30% because of changes in the vascular and interstitial spaces.

The urinary collecting system is dilated with hydronephrosis seen in up to 80% of pregnant women.

Hydronephrosis, although usually asymptomatic, predisposes women to serious ascending urinary tract infections. When severe, these infections may result in serious fetal complications and maternal complications such as septic shock and AKI.

Physiologic changes in the kidneys in pregnancy

Within weeks of conception, GFR increases by 40% to 60% and kidney blood flow by 80%.

These changes persist until the middle of the third trimester, whereas the creatinine production remains unchanged.

Total body water increases by 6 to 8 L, 4 to 6 L of which is extracellular and accounts for the edema of pregnancy.

This volume expansion depends on activation of the renin-aldosterone-angiotensin system.

There is cumulative sodium retention of up to 950 mmol on average.

Relaxin, a 6-kDa peptide produced by the corpus luteum, contributes to an increase in kidney blood flow, GFR, and solute clearance.

Effects of the gestational physiologic changes on laboratory parameters

An increase in clearance leads to a physiologic decrease in circulating creatinine, urea, and uric acid levels.

The average SCr level during pregnancy is 0.5 to 0.6 mg/dL and blood urea nitrogen level decreases to approximately 8 to 10 mg/dL.

Even a modest increase in SCr level to 1.0 mg/dL, although within the normal range, is reflective of kidney impairment.

An increase in protein excretion to 180 to 250 mg every 24 hours is seen in the third trimester because of an increase in filtered load combined with less efficient tubular reabsorption.^{9,10}

Normal protein excretion in pregnancy is less than 260 mg every 24 hours, with 1 + protein on urine dipstick considered abnormal.¹⁰

Women with preexisting proteinuria may exhibit an exaggeration of protein excretion in the second and third trimesters.

Traditionally, elevated uric acid has been used as a marker in preeclampsia, but its predictive value for diagnosis and prognosis of this condition has been mixed.¹¹ However, a recent study looking at uric acid in patients with gestational hypertension found it to be an accurate predictor of presence and severity of preeclampsia.¹²

Definitions of pregnancy-related acute kidney injury

Definitions used in the literature vary from a mild increase in SCr level to the need for dialysis.

Consensus definitions have been put forth for the definition of AKI in the general population (<http://kdigo.org/home/guidelines/>).

Some investigators have used the Risk, Injury, Failure, Loss, and End stage (RIFLE) criteria focusing on the change in SCr or GFR levels and urine output.¹³

One prospective study reported a higher RIFLE stage in PR-AKI to be related to unfavorable renal outcomes.¹⁴

High RIFLE class has discriminative power in predicting risk of mortality from AKI in obstetric ICU patients.¹⁵

The Acute Kidney Injury Network criteria, which use urine output and a change in SCr value of 26.2 mmol/L or 0.3 mg/dL from baseline to define the presence of AKI, is being used more often in pregnancy.¹⁶

Physiologic changes in pregnancy limit the use of these criteria or consensus definitions in PR-AKI.

Use of serum cystatin C has not been well studied in PR-AKI and cannot be recommended.

There is a need for a definition with high diagnostic accuracy that will allow early detection of AKI.

In the author's opinion, because of an increased solute clearance and the plasma volume expansion seen during pregnancy, a significant decline in GFR or a greater increase in the absolute SCr value is required to satisfy the current Acute Kidney Injury Network criteria of a 0.3- mg/dL increase in SCr level. Therefore, the current SCr criteria used in the general population probably may underestimate the occurrence of PR-AKI.

In the general population with CKD, the Modification of Diet in Renal Disease formula is widely used and yields results that are corrected for body surface area. In pregnancy, because body surface area changes, the results may be inaccurate. In one study, the Modification of Diet in Renal Disease formula underestimated GFR by more than 40 mL/min. Other methods such as measurement of serum cystatin C-based formulas have not been proven useful in pregnancy. Creatinine clearance measured with 24-hour urine collection remains the best approximate of the gold standard of insulin clearance, and remains the most validated method for measuring renal function in pregnancy.

The following pregnancy-associated AKI causes (**Box 2**) are discussed in some detail below.

1. Preeclampsia
2. Hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome
3. AFLP
4. TMA
5. Acute cortical necrosis (ACN)
6. Glomerular Disease

Box 1

Etiology of PR-AKI by gestational age

As in the general population, the causes of AKI in pregnant women are divided into 3 groups: prerenal, intrarenal, and postrenal causes.

Prerenal AKI (functional AKI) or acute tubular necrosis in the context of hyperemesis gravidarum or septic abortion are common causes when AKI occurs in the earlier stage of pregnancy.

In the later stages of pregnancy, when AKI is more frequent, it is usually associated with preeclampsia and other hypertensive disorders of pregnancy, acute fatty liver of pregnancy, HUS, and sepsis.¹⁷

Box 2**Etiologies of PR-AKI***Prerenal Causes^a*

- Pregnancy-related conditions
 - Hyperemesis gravidarum
 - Vomiting caused by preeclampsia, HELLP, and AFLP
 - Hemorrhage
 - Missed abortion
 - Septic abortion
 - Placental abruption
 - Placental previa
 - Uterine atony
 - Bleeding during surgery
 - Uterine laceration
 - Uterine perforation
- Pregnancy-unrelated conditions
 - Vomiting caused by infections such as UTI or sepsis, gastroenteritis
 - Pyelonephritis
 - Diuretic use
 - Congestive heart failure

Renal causes

- Pregnancy-related conditions
 - ATN, ACN
 - Preeclampsia
 - HELLP
 - AFLP
 - Amniotic fluid embolism
 - Pulmonary embolism
 - TMA
 - HUS
 - Preeclampsia
 - HELLP
 - AFLP
 - DIC
 - Worsening of existing glomerular disease
- Pregnancy-unrelated conditions
 - ATN
 - De novo glomerular diseases
 - Acute interstitial nephritis

Postrenal causes

- Pregnancy-related conditions
 - Bilateral hydronephrosis in rare cases
 - Trauma to the ureters and bladder during cesarean section
- Pregnancy-unrelated conditions
 - Bilateral ureteral obstruction caused by stones or tumor
 - Tubular obstruction (calcium or uric acid crystal induced)
 - Obstruction at the bladder outlet

AKI in kidney allograft

- Acute rejection
- ATN

- Acute interstitial nephritis, calcineurin inhibitor toxicity, recurrent disease, infections such as cytomegalovirus or BK virus
- Postinfectious glomerulonephritis

^a Can cause ATN and ACN.

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Preeclampsia is characterized by the new development of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation. Eclampsia, refers to the development of new-onset, generalized, tonic-clonic seizures or coma in a woman with preeclampsia. Both of these conditions are defined by the occurrence of fibrin and/or platelets thrombi in the microvasculature of organs, mainly the kidney and brain.

Hemolysis (with a microangiopathic anemia), elevated liver enzymes, and a low platelet count (HELLP) is considered by many, to be a severe form of preeclampsia, and may be seen in 10% to 20% of women with this condition. AKI caused by preeclampsia or eclampsia is rare in high-income countries, but can occur in 3% to 15% of cases of HELLP syndrome. It is a leading cause of PR-AKI, accounting for 40% to 60% of all cases.^{18–20} PR-AKI in HELLP syndrome, even severe forms requiring dialysis, usually has a favorable renal outcome, with less than 10% of patients, progressing to CKD, except in those patients with preexisting hypertension or renal disease.^{19,21,22}

Acute fatty liver of pregnancy is a rare condition, occurs in the third trimester of pregnancy, and is associated with preeclampsia in more than one-half of women, resulting in AKI in some. Differentiating it from HELLP may be difficult, but evidence of hepatic insufficiency, such as hypoglycemia or encephalopathy, and abnormalities in coagulation studies point toward AFLP. It may recur after pregnancies, especially if associated with long-chain 3-hydroxyacyl CoA dehydrogenase deficiency mutations.^{23,24} Supportive care and delivery of the fetus are the only treatments available.

Although rare in developed countries, ACN is responsible for a significant number of cases of AKI in parts of the world in which deliveries are remote from large cities and proper obstetric care is unavailable. ACN is usually seen when there is a catastrophic obstetric emergency such as placental abruption with massive hemorrhage, amniotic fluid embolism, disseminated intravascular coagulation (DIC), or any condition leading to severe renal ischemia. Women usually present with oliguria or anuria after the inciting event. Renal imaging shows hypoechoic areas on ultrasound or hypodense areas on computed tomography scan.

Significant breakthroughs have occurred in our understanding of the pathogenesis of TMA syndromes (**Box 3**), which led to a reclassification of this disorder²⁵ mainly into complement dysregulation TMA, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats)–deficient TMA, and TMA linked to other mechanisms (verotoxin and vascular endothelial growth factor deficiency), with a clear overlap between all these forms. This classification is more helpful for choosing the appropriate treatment than the older terms hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenia purpura (TTP). These syndromes require urgent treatment based on the pathophysiology, with TMAs

Box 3**Thrombotic microangiopathy syndromes***The primary TMA syndromes*

TTP; hereditary or acquired

Shiga toxin-mediated HUS

Drug-induced TMA syndromes

Complement-mediated TMA (hereditary or acquired)

Rare hereditary disorders of vitamin B12 metabolism or factors involved in hemostasis.

Secondary TMA—Caused by systemic disorders

Pregnancy-associated syndromes (eg, severe preeclampsia/HELLP syndrome)

Severe hypertension

Systemic infections and malignancies

Autoimmune disorders such as systemic lupus erythematosus or antiphospholipid antibody syndrome

Complications of hematopoietic stem cell or organ transplantation

associated with systemic disorders requiring therapy directed at the underlying disorder. TMA and other etiologies of AKI may occur in the transplanted kidney during pregnancy and require input and close monitoring from the transplant nephrologist ([Table 1](#)).

Pregnancy-related thrombotic microangiopathy

Etiology of pregnancy-related TMA (P-TMA) is similar to other types of TMA.

P-TMA may be associated with ADAMTS13 deficiency, complement dysregulation, or other mechanisms.

The timing of presentation seems to vary with the type of TMA.

ADAMTS13 deficiency–related P-TMA occurs mainly during the second and third trimesters of pregnancy.²⁶

There is a progressive decrease in ADAMTS13 level and a parallel increase in von Willebrand factor antigen during normal pregnancy^{27,28} with ADAMTS13 activity/von Willebrand factor antigen ratio reaching a nadir during the second and third trimesters.

This potentiates the inhibitory effect of anti-ADAMTS13 autoantibodies, leading to TMA.

P-TMA caused by complement pathway dysregulation occurs mainly (80% of cases) during the postpartum period.

Infections and bleeding, which frequently complicate the postpartum period, may trigger complement activation leading to TMA.

Complement pathway dysregulation may be involved in the pathogenesis of pregnancy complications beyond atypical HUS (aHUS). It has been recently linked to autoimmune (lupus/antiphospholipid syndrome–associated preeclampsia) and the antiphospholipid syndrome–associated obstetric complications and nonimmune

Disease Manifestations and Management	Severe Preeclampsia/HELLP	AFLP	TTP/HUS	SLE/APLS	aHUS
Timing of onset					
2nd trimester	+	+	++	+	+
3rd trimester	++	++	+	+	+
Postpartum	+	-	+	+	++
Signs and symptoms					
Fever	-	-	+	+	+
HTN	+++	++	+	++	+
Neurologic symptoms	+	+	++	+	-
Purpura	-	-	++	+	++
Laboratory abnormalities					
AKI	+	++	+++	++	+++
Hemolytic anemia	++	+	+++	++	+++
Thrombocytopenia	++	+	+++	+	+++
Transaminitis	++	+++	+	-	+
DIC	+	++	-	+	-
Elevated PT	++	+++	-	-	-
Hypoglycemia	-	++	-	-	-
ADAMTS13 deficiency	+	-	++	-	+
Treatment					
Delivery/supportive	+++	+++	-	-	-
Plasmapheresis	-	-	+++	+	+++
Steroids	+ ^a	+ ^a	+/-	+++	-

+ indicates mild/occasionally; ++ indicates moderate/sometimes; +++ indicates severe/always; +/– indicates limited data.

Abbreviations: HTN, hypertension; PT, prothrombin time; SLE/APLS, systemic lupus erythematosus/antiphospholipid syndrome.

^a Indicated for fetal lung maturation.

From Acharya A, Santos J, Linde B, et al. Acute kidney injury in pregnancy—current status. *Adv Chronic Kidney Dis* 2013;20(3):218; with permission.

preeclampsia.²⁹ Complement blockade is effective in ameliorating preeclampsia features in a murine model.^{30–32} Complement gene mutations similar to those seen in aHUS have been identified in some forms of HELLP syndrome.³³

Management of Pregnancy-related Acute Kidney Injury Requires a Multidisciplinary Approach

Although baseline assessment of renal function is not part of routine practice, having a baseline assessment of renal function is invaluable. This strategy aids in early identification of those at risk and helps make an accurate and timely diagnosis of PR-AKI (Fig. 1).

Diagnostic testing and treatment varies based on the suspected underlying diagnosis and the clinical scenario.

Breakthroughs in our understanding of the pathogenic mechanisms underlying many of the pregnancy-associated conditions, such as imbalance of angiogenic

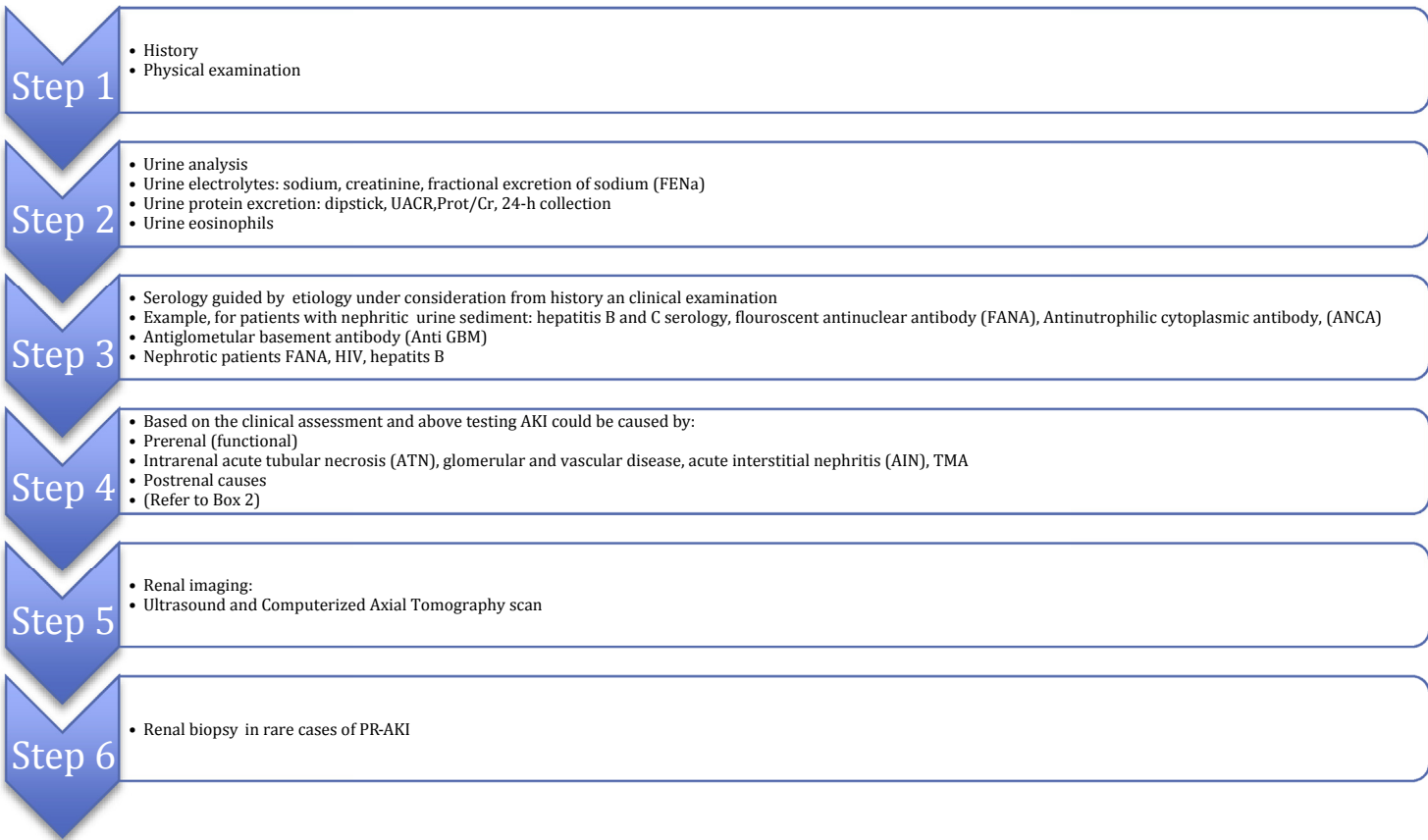


Fig. 1. Basic flow chart for PR-AKI workup.

factors in preeclampsia and pathogenetic mechanisms in thrombotic microangiopathies, hold promise and will undoubtedly enable strides in management of these conditions in the near future.

Tools for evaluation of a patient with pregnancy-related acute kidney injury

Evaluation of a pregnant patient with AKI is similar to that in the general population.

Prerenal, intrarenal, and postrenal causes of AKI are sought, based on history and physical examination.

Urinalysis and urine electrolytes are evaluated using the general principles of evaluating AKI.¹³

These parameters, particularly the use of urine electrolytes, need exploration in pregnancy because many physiologic mechanisms promote sodium reabsorption and natriuresis at different stages of pregnancy.

Although proteinuria is removed from the recent American Congress of Obstetricians and Gynecologists definition of preeclampsia, it plays an important role in the diagnosis of primary glomerular disease and in severe and superimposed preeclampsia.

The distinction between renal disease and preeclampsia is extremely important because it affects clinical management.

Proteinuria can be assessed by using the urinary dipstick method, 24-hour urine collection, and protein/creatinine ratio on a random sample.

Urine albumin/creatinine ratio (ACR) can be performed using an automated analyzer, allowing immediate point-of-care testing.

Ultrasound and Computerized Axial Tomography scan of the kidney as required.

Renal biopsy

Evaluation of proteinuria

Twenty-four-hour urine collection, although the most accurate for quantifying urinary protein, is cumbersome for the patient and has the possibility of incomplete collection.

Obstetric caregivers are using the protein/creatinine ratio more frequently.

Many studies have confirmed the reliability of spot protein/creatinine ratio in pregnancy and it has become accepted as the test of choice for quantifying proteinuria in pregnancy.^{34–36}

ACR has the potential to supplant urinary dipstick as a rapid and accurate screening method for proteinuria in routine obstetric care.³⁷

Although ACR and protein/creatinine ratio are well correlated we recommend that clinicians keep the cost in consideration and use the test with which they are familiar.³⁸

Role of renal biopsy during pregnancy

There is reluctance to perform kidney biopsies in pregnancy because of the potential risk of complications such as major bleeding, severe obstetric complications, and early preterm deliveries.

The risk/benefit ratio varies according to gestational age.

Prior studies of renal biopsies in preeclampsia show that histologic changes do not reflect the severity of preeclampsia.

The risks and advantages of empirical therapeutic approaches versus kidney biopsy must be considered on a case-by-case basis.

It is prudent to limit the procedure to women with a suspicion of any condition that is associated with rapid worsening of renal function and is severe enough to warrant urgent treatment or a change in therapy.

In cases of TMA, kidney biopsy does not help identify the etiology of the TMA.³⁹

The most common lesion in women with HELLP-associated AKI is glomerular endotheliosis, similar to the lesions in preeclampsia and not that of TMA.

Novel noninvasive diagnostic approaches

These tests may change the indications for kidney biopsy in pregnancy in the future.

The angiogenic factors such as soluble fms-like tyrosine kinase-1, placental growth factor, and soluble endoglin are used as diagnostic and predictive markers for preeclampsia^{40,41}

Fms-like tyrosine kinase-1/placental growth factor ratio^{28,42} is used to differentiate renal disease from preeclampsia.

Anti-PLA2R (M-type phospho-lipase A₂ receptor) for detection and monitoring disease activity in membranous nephropathy⁴³

Soluble urokinase-type plasminogen activator receptor to diagnose focal segmental glomerulosclerosis

Analyzing the patterns of proteinuria and identifying discriminating proteins using proteomic techniques

Other novel serum or urine markers of glomerular diseases, preeclampsia, and acute kidney injury that were not available earlier⁷⁶⁻⁷⁹

Strategies for prevention of pregnancy-related acute kidney injury

Address predisposing factors such as hyperemesis gravidarum in a timely fashion to avoid functional renal injury.

It is important to minimize the use of nonsteroidal anti-inflammatory drugs especially in women at risk for AKI and to avoid them in those with established AKI.

Avoid unnecessary medications or withdraw medications that may be suspicious of causing acute interstitial nephritis. Proton pump inhibitors are associated with increased risk of AKI from acute interstitial nephritis, in the general population.

Ascending infections from urinary tract infection (UTIs) in pregnancy is not uncommon. Pregnant women may become quite ill and are at risk for both medical and obstetric complications from pyelonephritis.

Infectious Diseases Society of America recommends screening all pregnant women for asymptomatic bacteriuria at least once in early pregnancy, especially in women at high risk or those with known anatomic renal anomalies.

Treat UTI with appropriate antibiotics after obtaining urine culture. Progression to pyelonephritis not only has detrimental effects on the fetus but also increases risk of AKI in the mother.

Refer to US Food and Drug Administration (FDA) drug class before prescribing.

Treatment of Pregnancy-Related Acute Kidney Injury

Because of the heterogeneity of the etiology of PR-AKI, therapy must be tailored to the underlying condition. Strategies are presented as supportive care and targeted therapies.

Supportive care

Optimal fluid management and the selection of the specific type of fluid should be based on indications and keeping in mind contraindications and aiming to minimize toxicity.

Volume repletion with isotonic crystalloid solutions is indicated in women with blood loss.

The rate and type of fluids used for volume correction depends on the severity of volume depletion. Isotonic solutions are used for initial resuscitation when hypovolemia is present. Balanced or physiologic solutions are gaining favor based on recent studies in the general population, for maintenance.

Concurrent abnormalities in other electrolytes, such as serum sodium, and the presence of underlying kidney or cardiac disease also influence the choice and rate of fluid administration.

Close monitoring for signs and symptoms of electrolyte abnormalities is essential in those with PR-AKI.

Hypermagnesemia may develop in patients with preeclampsia and eclampsia who have AKI when magnesium sulfate is being administered. This is especially a concern in those with oliguria or anuria. Frequent assessment of serum magnesium level is recommended.

Use of Renal Replacement Therapy in Pregnancy-related Acute Kidney Injury

The reported use of RRT in PR-AKI ranges widely depending on the population reported.

One study from the developed world reported less than 1 in 10,000 to 15,000 pregnancies needing RRT; another from a developing nation found that up to 60% of their PR-AKI patients required RRT.^{44,45}

Both intermittent hemodialysis and peritoneal dialysis have been used successfully.⁴⁶

For critically ill and hemodynamically unstable women with PR-AKI, continuous RRT modalities should be considered. Continuous RRT has theoretic benefits of lower hemodynamic and volume shifts.

Data on timing of initiation (**Box 4**) are lacking, but a lower threshold for initiating RRT has been proposed in PR-AKI, similar to that in pregnant women with CKD. This is in order to decrease the unwanted effects of uremia on the fetus, such as polyhydramnios, developmental delay, and preterm birth.^{13,47,48}

Box 4

Indications for starting renal replacement therapy in pregnancy-related acute kidney injury are similar to those in the nonpregnant population

Acidosis

Uremia

Electrolyte disturbance, such as hyperkalemia, hypermagnesemia and hypercalcemia that are refractory to medical management

Fluid overload

Intoxications

Targeted Therapy for Pregnancy-related Acute Kidney Injury

In cases of acute tubular necrosis (ATN), there is no specific therapy, and supportive care is practiced while the injury runs its course. Oliguria indicates more severe injury and requires diuretic use to increase urine output. This may delay the need for RRT but does not prevent ATN or shorten the duration of renal failure and is not recommended for this purpose (KIDIGO 2012). In patients with ATN, a positive fluid balance is an independent predictor of increased mortality in several prospective ICU studies.⁴⁹

Acute interstitial nephritis, which is characterized by an inflammatory infiltrate in the kidney interstitium, is most commonly caused by drugs. Onset of AKI is temporally related to the initiation of a new drug. Withdrawal of the drug usually results in improvement of renal function in 5 to 7 days, but treatment with glucocorticoids is necessary in some. Other less frequent etiologies include infection, sarcoidosis, or uveitis syndrome and require appropriate workup.

There is no specific therapy for acute cortical necrosis. Supportive care is provided, and RRT is required in many cases. Partial or complete recovery may be seen in 20% to 40% of women.⁵⁰

Glomerular disease may be preexisting or may develop *de novo* during pregnancy. Treatment is based on expert opinion, as little evidence-based data are available. Differentiating from preeclampsia is important, and many of these women subsequently have superimposed preeclampsia. In biopsy-proven glomerulonephritis, steroid and immunosuppressive therapy may be warranted. Use of immunosuppression in pregnancy is only indicated for life-threatening maternal illness and agents with the most desirable safety profile and FDS drug class are used.

The mainstay of treatment in pregnancies complicated by preeclampsia/eclampsia, HELLP syndrome, and AFLP is delivery of the fetus⁵¹ guided by the gestational age, maternal and fetal condition, and the severity of preeclampsia. Corticosteroids should be considered if preterm delivery is likely. Control of blood pressure plays an important role to reduce maternal morbidity.

In the last decade, our management of hypertension in pregnancy has dramatically improved. Although there is ongoing debate on what level of hypertension to initiate therapy, treatment of severe hypertension with systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mm Hg is always recommended to reduce the risk of maternal complications such as posterior reversible encephalopathy syndrome and stroke. Recent data suggest that treatment may be associated with maternal benefits without excess risk to the fetus.^{52,53}

Although all antihypertensive drugs cross the placenta, there are many effective antihypertensive agents with an acceptable safety profile in pregnancy and during breast feeding. The choice of drug depends on the acuity and severity of hypertension and whether parenteral or oral therapy is used; angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and direct renin inhibitors are contraindicated in pregnancy because of their effects on fetal development.

The other crucial therapy is the use of magnesium sulfate with an aim to prevent and treat seizures. The kidneys are the main route of excretion of magnesium, and dose adjustment is necessary when PR-AKI develops. In women with established PR-AKI, additional serum magnesium level monitoring every 6 hours is recommended to avoid neuromuscular and cardiovascular toxicity. Severe magnesium toxicity may require RRT.

Apart from delivery of the fetus, the use of steroids and plasma exchange for treatment of severe HELLP syndrome is controversial.^{54,55} As the spectrum of pregnancy disorders linked to complement dysregulation/activation expands and the link

confirmed, complement inhibition may represent a potential treatment for severe HELLP syndrome.

Pregnancy is a potent trigger for TMA in predisposed women and P-TMA is considered a secondary form of TMA that is associated with a high morbidity and mortality (up to 10%).⁵⁶ It accounts for 8% to 18% of all cases of TMA.^{26,57–59} In the French aHUS registry, 1 of 5 women presented with aHUS at the time of pregnancy.²⁶

Treatment of ADAMTS13 deficiency-related pregnancy-related thrombotic microangiopathy

Plasma therapy aims to restore a significant enzymatic activity (>10%) through: clearance of autoantibodies using plasma exchanges (PEX); restoration of ADAMTS 13 with fresh frozen plasma infusions in case of constitutional ADAMTS13 deficiency

PEX should be initiated as soon as possible.⁶⁰ both in established cases and when it is not possible to differentiate between preeclampsia, HELLP, and AFLP.

PEX is performed daily until a platelet count of greater than $150 \times 10^9/L$ is achieved for at least 3 days and until the serum lactate dehydrogenase level normalizes.

For TTP presenting in the first trimester, regular plasma exchange with close monitoring may allow for continuation of pregnancy.

Use of corticosteroids is not well supported.

Delivery is recommended in cases that do not respond to PEX.⁶¹

Concern for fetal toxicity and long-term effects on the neonates limits the use of rituximab, a B-cell-depleting antibody that is a second-line agent for TTP.^{62,63}

The FDA has given rituximab a pregnancy label C.

Its use during pregnancy should be decided on a case-by-case basis depending on the potential benefits and risks of such treatment.

Treatment of complement dysregulation thrombotic microangiopathy

Aim to rapidly inhibit complement cascade activation using complement modulators.

Early use probably improves renal recovery.

Response to plasma therapy may not be optimal.

Eculizumab, a monoclonal humanized IgG that prevents the generation of C5a, and C5b, which initiates the formation of the membrane attack complex^{64,65} and blocks the common terminal activation is currently the only available agent.

The standard eculizumab regimen includes 4 weekly 900-mg infusions followed by 1200-mg infusions every 2 weeks.

C5 inhibition can be easily monitored using total complement hemolytic assay with an aim of keeping it less than 20%.

Its prohibitive cost makes treatment impractical in many parts of the world.

Precautions before use of eculizumab

C5 inhibition increases the risk of infections with meningococcus.

Antimeningococcal vaccine should be administered before the start of eculizumab.

Additional oral antibiotic prophylaxis may be required during the period of eculizumab treatment and while waiting for the vaccine to take effect.

Pregnancy can increase the overall risk of TMA relapse, and a relapse rate of around 30% has been reported.^{63,66}

The monitoring of ADAMTS13 levels during pregnancy may help identify patients at high risk of TMA relapse. Some investigators have even advocated the use, early in pregnancy, of PEX in pregnant women with known ADAMTS13 deficiency, to maintain an enzymatic activity greater than 10%.⁶⁷ However, there are no clear evidence-based guidelines for prophylactic treatment of ADAMTS13 deficiency TMA during pregnancy.

Complement dysregulation is not a contraindication for pregnancy, but genetic testing of patients to identify their potential risk of P-TMA is encouraged. Prepregnancy counseling of patients with complement gene abnormalities is crucial. The risk of recurrence varies based on the type of genetic mutation (eg, high in *CFH* and *C3* mutations versus lower in *CFI* and membrane-cofactor protein).

A major limitation in improving outcome of AKI has been the lack of common standards for diagnosis and classification. The best way to improve outcomes of PR-AKI is prevention and early detection.

SUMMARY

In all, the incidence of P-AKI has probably decreased, but its fetal and maternal morbidity remain unacceptably high.

Pregnancy hypertensive complications, notably HELLP syndrome, are the leading cause of P-AKI.

P-TMA is a clinically challenging cause of P-AKI.

Several breakthroughs in our understanding of different mechanisms underlying P-TMA and preeclampsia have already led to a better treatment of these patients.

REFERENCES

1. Stratta P, Besso L, Canavese C, et al. Is pregnancy-related acute renal failure a disappearing clinical entity? *Ren Fail* 1996;18(4):575–84.
2. Prakash J, Niwas SS, Parekh A, et al. Acute kidney injury in late pregnancy in developing countries. *Ren Fail* 2010;32(3):309–13.
3. Mehrabadi A, Liu S, Bartholomew S, et al. Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study. *BMJ* 2014;349:g4731.
4. Mehrabadi A. Investigation of a rise in obstetric acute renal failure in the United States, 1999-2011. *Obstet Gynecol* 2016;127(5):899–906.
5. 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.
6. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA* 2015;313(8):837–46.
7. Sibai BM, Villar MA, Mabie BC. Acute renal failure in hypertensive disorders of pregnancy. Pregnancy outcome and remote prognosis in thirty-one consecutive cases. *Am J Obstet Gynecol* 1990;162(3):777–83.
8. Vikse BE. Pre-eclampsia and the risk of kidney disease. *Lancet* 2013;382(9887):104–6.
9. Higby K, Suiter CR, Phelps JY, et al. Normal values of urinary albumin and total protein excretion during pregnancy. *Am J Obstet Gynecol* 1994;171(4):984–9.
10. Airoidi J, Weinstein L. Clinical significance of proteinuria in pregnancy. *Obstet Gynecol Surv* 2007;62(2):117–24.

11. Johnson RJ, Kanbay M, Kang DH, et al. Uric acid: a clinically useful marker to distinguish preeclampsia from gestational hypertension. *Hypertension* 2011; 58(4):548–9.
12. Roberts JM, Bodnar LM, Lain KY, et al. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. *Hypertension* 2005; 46(6):1263–9.
13. Gammill HS, Jeyabalan A. Acute renal failure in pregnancy. *Crit Care Med* 2005; 33(Suppl 10):S372–84.
14. Arrayhani M, El Youbi R, Sqalli T. Pregnancy-related acute kidney injury: experience of the nephrology unit at the university hospital of fez, morocco. *ISRN Nephrol* 2013;2013:109034.
15. Kamal EM, Behery MM, Sayed GA, et al. RIFLE classification and mortality in obstetric patients admitted to the intensive care unit with acute kidney injury: a 3-year prospective study. *Reprod Sci* 2014;21(10):1281–7.
16. Gurrieri C, Garovic VD, Gullo A, et al. Kidney injury during pregnancy: associated comorbid conditions and outcomes. *Arch Gynecol Obstet* 2012;286(3):567–73.
17. Machado S, Figueiredo N, Borges A, et al. Acute kidney injury in pregnancy: a clinical challenge. *J Nephrol* 2012;25(1):19–30.
18. Drakeley AJ, Le Roux PA, Anthony J, et al. Acute renal failure complicating severe preeclampsia requiring admission to an obstetric intensive care unit. *Am J Obstet Gynecol* 2002;186(2):253–6.
19. Gul A, Aslan H, Cebeci A, et al. Maternal and fetal outcomes in HELLP syndrome complicated with acute renal failure. *Ren Fail* 2004;26(5):557–62.
20. Haddad B, Barton JR, Livingston JC, et al. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome versus severe preeclampsia: onset at < or =28.0 weeks' gestation. *Am J Obstet Gynecol* 2000;183(6):1475–9.
21. Sibai BM, Ramadan MK, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 1993;169(4):1000–6.
22. Selcuk NY, Odabas AR, Cetinkaya R, et al. Outcome of pregnancies with HELLP syndrome complicated by acute renal failure (1989-1999). *Ren Fail* 2000;22(3):319–27.
23. Wilcken B, Leung KC, Hammond J, et al. Pregnancy and fetal long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency. *Lancet* 1993;341(8842):407–8.
24. Schoeman MN, Batey RG, Wilcken B. Recurrent acute fatty liver of pregnancy associated with a fatty-acid oxidation defect in the offspring. *Gastroenterology* 1991;100(2):544–8.
25. Fakhouri F, Fremeaux-Bacchi V. Does hemolytic uremic syndrome differ from thrombotic thrombocytopenic purpura? *Nat Clin Pract Nephrol* 2007;3(12):679–87.
26. Fakhouri F, Roumenina L, Provot F, et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol* 2010;21(5):859–67.
27. Mannucci PM, Canciani MT, Forza I, et al. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood* 2001;98(9):2730–5.
28. Verlohren S, Galindo A, Schlembach D, et al. An automated method for the determination of the sFlt-1/PIGF ratio in the assessment of preeclampsia. *Am J Obstet Gynecol* 2010;202(2):161.e1-11.

29. Salmon JE, Heuser C, Triebwasser M, et al. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. *PLoS Med* 2011;8(3):e1001013.
30. Shamonki JM, Salmon JE, Hyjek E, et al. Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. *Am J Obstet Gynecol* 2007;196(2):167.e1-5.
31. Redecha P, Tilley R, Tencati M, et al. Tissue factor: a link between C5a and neutrophil activation in antiphospholipid antibody induced fetal injury. *Blood* 2007;110(7):2423–31.
32. Qing X, Redecha PB, Burmeister MA, et al. Targeted inhibition of complement activation prevents features of preeclampsia in mice. *Kidney Int* 2011;79(3):331–9.
33. Fakhouri F, Jablonski M, Lepercq J, et al. Factor H, membrane cofactor protein, and factor I mutations in patients with hemolysis, elevated liver enzymes, and low platelet count syndrome. *Blood* 2008;112(12):4542–5.
34. Cote AM, Brown MA, Lam E, et al. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. *BMJ* 2008;336(7651):1003–6.
35. Cheung HC, Leung KY, Choi CH. Diagnostic accuracy of spot urine protein-to-creatinine ratio for proteinuria and its association with adverse pregnancy outcomes in Chinese pregnant patients with pre-eclampsia. *Hong Kong Med J* 2016;22(3):249–55.
36. Nischintha S, Pallavee P, Ghose S. Correlation between 24-h urine protein, spot urine protein/creatinine ratio, and serum uric acid and their association with fetomaternal outcomes in preeclamptic women. *J Nat Sci Biol Med* 2014;5(2):255–60.
37. Wilkinson C, Lappin D, Vellinga A, et al. Spot urinary protein analysis for excluding significant proteinuria in pregnancy. *J Obstet Gynaecol* 2013;33(1):24–7.
38. Cade TJ, de Crespigny PC, Nguyen T, et al. Should the spot albumin-to-creatinine ratio replace the spot protein-to-creatinine ratio as the primary screening tool for proteinuria in pregnancy? *Pregnancy Hypertens* 2015;5(4):298–302.
39. Abraham KA, Kennelly M, Dorman AM, et al. Pathogenesis of acute renal failure associated with the HELLP syndrome: a case report and review of the literature. *Eur J Obstet Gynecol Reprod Biol* 2003;108(1):99–102.
40. Sunderji S, Gaziano E, Wothe D, et al. Automated assays for sVEGF R1 and PIGF as an aid in the diagnosis of preterm preeclampsia: a prospective clinical study. *Am J Obstet Gynecol* 2010;202(1):40.e1-7.
41. Hadker N, Garg S, Costanzo C, et al. Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective. *J Med Econ* 2010;13(4):728–37.
42. Rolfo A, Attini R, Nuzzo AM, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. *Kidney Int* 2013;83(1):177–81.
43. Fresquet M, Jowitt TA, Gummadova J, et al. Identification of a major epitope recognized by PLA2R autoantibodies in primary membranous nephropathy. *J Am Soc Nephrol* 2015;26(2):302–13.
44. Najar MS, Shah AR, Wani IA, et al. Pregnancy related acute kidney injury: A single center experience from the Kashmir Valley. *Indian J Nephrol* 2008;18(4):159–61.
45. Clark SL. *Handbook of critical care obstetrics*. Boston: Blackwell Scientific Publications; 1994.

46. Chou CY, Ting IW, Lin TH, et al. Pregnancy in patients on chronic dialysis: a single center experience and combined analysis of reported results. *Eur J Obstet Gynecol Reprod Biol* 2008;136(2):165–70.
47. Holley JL, Reddy SS. Pregnancy in dialysis patients: a review of outcomes, complications, and management. *Semin Dial* 2003;16(5):384–8.
48. Dragun D. Acute kidney failure during pregnancy and postpartum. Management of acute kidney problems. Heidelberg (Germany): Springer-Verlag; 2010. p. 445–58.
49. Grams ME, Estrella MM, Coresh J, et al. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol* 2011;6(5):966–73.
50. Matlin RA, Gary NE. Acute cortical necrosis. Case report and review of the literature. *Am J Med* 1974;56(1):110–8.
51. Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in pregnancy. *J Am Soc Hypertens* 2010;4(2):68–78.
52. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;(2):CD002252.
53. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372(5):407–17.
54. Katz L, de Amorim MM, Figueiroa JN, et al. Postpartum dexamethasone for women with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a double-blind, placebo-controlled, randomized clinical trial. *Am J Obstet Gynecol* 2008;198(3):283.e1-8.
55. Eckford SD, Macnab JL, Turner ML, et al. Plasmapheresis in the management of HELLP syndrome. *J Obstet Gynaecol* 1998;18(4):377–9.
56. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood* 2003;102(1):60–8.
57. Veyradier A, Obert B, Houllier A, et al. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. *Blood* 2001;98(6):1765–72.
58. Morigi M, Galbusera M, Gastoldi S, et al. Alternative pathway activation of complement by Shiga toxin promotes exuberant C3a formation that triggers microvascular thrombosis. *J Immunol* 2011;187(1):172–80.
59. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010;5(10):1844–59.
60. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood* 2010;116(20):4060–9.
61. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol* 2012;158(3):323–35.
62. Fakhouri F, Vernant JP, Veyradier A, et al. Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient thrombotic thrombocytopenic purpura: a study of 11 cases. *Blood* 2005;106(6):1932–7.
63. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood* 2011;118(7):1746–53.
64. Kaplan M. Eculizumab (Alexion). *Curr Opin Investig Drugs* 2002;3(7):1017–23.

65. Woodruff TM, Nandakumar KS, Tedesco F. Inhibiting the C5-C5a receptor axis. *Mol Immunol* 2011;48(14):1631–42.
66. Kremer Hovinga JA, Vesely SK, Terrell DR, et al. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood* 2010;115(8):1500–11 [quiz: 1662].
67. Scully M, Starke R, Lee R, et al. Successful management of pregnancy in women with a history of thrombotic thrombocytopenic purpura. *Blood Coagul Fibrinolysis* 2006;17(6):459–63.