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Acute Kidney Injury in Pregnancy

WG van Hougenhouck-Tulleken, N Roche, AZ Muranda
Steve Biko Academic Hospital and the University of Pretoria, Pretoria, South Africa

Abstract
Pregnancy related acute kidney injury (PrAKI) is a relatively rare syndrome, and is associated with many pregnancy-unique diseases. Due to the physiological changes of pregnancy, PrAKI is difficult to diagnose, hard to predict and often diagnosed after significant damage to the kidney has manifest. In developing countries, the incidence is increased and the outcomes are poorer. Long term consequences to the mother are severe and underappreciated. An understanding of PrAKI can only be achieved once the dynamic physiological changes of pregnancy are understood and merged with insight into acute kidney injury.

Keywords: Pregnancy; Acute Kidney Injury

Introduction

Pregnancy related acute kidney injury (PrAKI) is a complex disease entity that appears to be both poorly understood and poorly treated. There are multiple reasons that account for this, including a lack of an international definition of acute kidney injury (AKI) in pregnancy, the physiological changes in pregnancy that often mask AKI and lack of caregiver insight into PrAKI. This ultimately leads to delayed diagnosis.[1] Acute kidney injury is an acute (< seven days) deterioration in renal function, resulting in the accumulation of nitrogenous waste products, electrolyte homeostatic aberrations and extracellular volume abnormalities.[2] Standardised definition and staging of AKI in non-pregnant individuals published by the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup are shown in Table 1.[2] The KDIGO definition is an amalgamation of the previous AKI definitions forwarded by the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN) groups.[3,4]

Traditional teaching regarding renal failure have highlighted the perils of severe renal failure (arrhythmias, pericarditis, encephalopathy and anuria), while the modest changes seen in AKI are glossed over or even ignored.[2,5] New data have revealed that AKI, with even modest rises in creatinine, have a profound effect. Chertow et al found that clinical outcomes, regardless of disease process, were related directly to the severity of AKI.[5] (Table 2)

While this may be intuitive to some, Chertow et al. highlights the importance of recognising and treating AKI early, as mortality increases significantly even with relatively small increases in creatinine. The significance of this is heightened with PrAKI, as a serum creatinine increase of 26.5 µmol/L from baseline in a pregnant patient may be reported as within the normal reference range by the laboratory. This is as a result of the marked physiological changes occurring in the pregnant patient due to the effects of the feto-placetal unit. Estimated glomerular filtration rate (eGFR) increases on average by 50%, resulting in an overall decrease in serum creatinine.[6]

Correspondence
W van Hougenhouck-Tulleken
Steve Biko Academic Hospital
Dr Savage Road, Pretoria
email: westulleken@gmail.com

Table 1: KDIGO staging of AKI

Stage	Creatinine	Urine output
1	1.5 – 1.9 times baseline, or ≥ 26.5µmol/l increase	< 0.5ml/kg/hr for six to twelve hours
2	2.0 – 2.9 times baseline	< 0.5ml/kg/hr for ≥ twelve hours
3	3.0 or more times baseline, or creatinine ≥ 353.6 µmol/l, or initiation of RRT, or in patients < 18 years, decrease in eGFR to 35ml/min per 1.73 m^2	< 0.3ml/kg/hr for ≥ twenty four hours, or anuria for ≥ twelve hours

RRT: Renal replacement therapy. eGFR: Estimated glomerular filtration rate. From Kellum et al., 2012.

Table 2: Relationship between serum creatinine increase and risk of all-cause mortality

Increase in serum creatinine from baseline	Unadjusted all-cause mortality OR (95% CI)
26.5 µmol/L	6.9 (5.2 to 9.0)
44.2 µmol/L	11.1 (8.7 to 14.2)
88.4 µmol/L	19.9 (15.1 to 26.1)
176.8 µmol/L	36.4 (24.3 to 54.6)

OR: Odds ratio. CI: Confidence interval. From Chertow et al., 2005.

Renal changes in pregnancy

Pregnancy results in profound physiological and anatomical changes in the mother. While the effects are global, changes specific to the nephrological system are marked. Anatomically, the kidney in pregnancy increases in size by up to 1 - 1.5cm, and in volume by up to 30%. This is due to increases in renal vascular volume, interstitial volume expansion and increased renal plasma flow.[7,8] Hydroureter and hydronephrosis are common, occurring in up to 80% of pregnant women, and is more pronounced on the right.[1,9] This may lead to urinary stasis, and may be a factor in the increased frequency of asymptomatic bacteriuria and urinary tract infections seen in pregnant women. Estimated GFR increases within one month of conception and remains elevated throughout pregnancy.[6] The increased eGFR is as a result of the elevated cardiac output and renal blood flow seen in pregnancy.[10] Cardiac output increases by up to 50% in pregnancy, and is due to an increase in preload (due to an increase in blood volume, mediated by an increase in the renin-angiotensin-aldosterone system) and a decrease in afterload. The decreased afterload is due to decrease in systemic vascular resistance from a relative resistance to vasopressors (angiotensin II, norepinephrine and possibly arginine vasopressin) and increased production of vasodilators (endothelial prostacyclins and nitrous oxide).[11-14] Resultant increases in the total systemic volume and eGFR alter the normal values for most serological tests, as shown in Table 3.

As stated previously, the eGFR in a pregnant patient

Table 3: Normal values for selected serological tests in the pregnant and non-pregnant state

	Non-pregnant Adult*	First Trimester	Second Trimester	Third Trimester
Sodium (mmol/L)	136 - 146	133 - 148	129 - 148	130 - 148
Potassium (mmol/L)	3.5 - 5.0	3.6 - 5.0	3.3 - 5.0	3.3 - 5.1
Chloride (mmol/L)	102 - 109	101 - 105	97 - 109	97 - 109
Bicarbonate (mmol/L)	22 - 30	20 - 24	20 - 24	20 - 24
Urea (mmol/L)	2.50 - 7.14	2.50 - 4.30	1.07 - 4.64	1.07 - 3.93
Creatinine (µmol/L)	44.2 - 79.6	35.4 - 61.9	35.4 - 70.7	35.4 - 79.6
Osmolality (mOsm/kg H_20)	275 - 295	275 - 280	276 - 289	278 - 280
Calcium, ionized (mmol/L)	2.18 - 2.55	2.20 - 2.65	2.05 - 2.25	2.05 - 2.43
Magnesium (mmol/L)	0.62 - 0.95	0.66 - 0.90	0.62 - 0.90	0.45 - 0.90
Phosphate (mmol/L)	0.81 - 1.39	1.00 - 1.49	0.81 - 1.49	0.90 - 1.49
Uric acid (mmol/L)	0.15 - 0.33	0.12 - 0.25	0.14 - 0.29	0.18 - 0.37
Effective renal plasma flow (mL/min)	492 - 696	696 - 985	612 - 1170	595 - 945
Glomerular filtration rate (GFR) (mL/min)	106 - 132	131 - 166	135 - 170	117 - 182
24-h urinary protein excretion (mg/24 h)	< 150	19 - 141	47 - 186	46 - 185

*Values are for adult females. 24-h: Twenty-four hour. From Abbassi-Ghanavati et al., 2009.

can increase by up to 50%, decreasing serum creatinine on average by 26.5 µmol/L. Hence PrAKI can be present with a normal serum creatinine and eGFR.[6] This is compounded by the fact that baseline values are not generally known before presentation to the health care provider (HCP). Hence, knowledge of the common causes of PrAKI, strong clinical suspicion and vigilance are needed when treating pregnant patients.

Epidemiology of acute kidney injury in pregnancy

The true epidemiology of PrAKI is hard to quantify, as an international definition of PrAKI is lacking. However, from various reports, the incidence of PrAKI appears to be divided along socioeconomic lines: some developed countries report a PrAKI incidence of 1 in 20 000 (0.005%), whereas other developing countries report a PrAKI incidence to range between 4% to 36%. The increased incidence of PrAKI in developing countries appears to be due to sepsis, particularly that related to illegal abortions.[1,15-17] Pregnancy related AKI appears to be more common in the third trimester, with up to 72.7% of PrAKI developing in the third trimester in one study.[18]

Pregnancy related AKI is associated with poorer pregnancy outcomes, with an increase in the number of caesarean sections performed, an increase in preterm deliveries, stillbirths and overall lower apgars in children of mothers with PrAKI. Additionally, PrAKI shows a trend towards a lower birth weight.[18]

Causes of acute kidney injury in pregnancy

Pregnancy related AKI represents a unique disease process. While any disease process that causes AKI in a non-pregnant patient can cause PrAKI, there are additional causes of AKI that are unique to the pregnant state. The causes of PrAKI can be divided into those that occur before twenty weeks of gestation, and those that occur thereafter. Furthermore, these can be classed as pre-, intra- or post-renal causes.

The most common causes of PrAKI before twenty weeks gestation include sepsis (urosepsis, septic abortion or pneumonia) and hypovolaemia (hyperemesis gravidarum and gastroenteritis).[1] The resultant hypotension can cause acute tubular necrosis (ATN) when the mean arterial pressure falls beneath a critical threshold, where autoregulation of renal blood flow cannot be maintained

Table 4: Summary of PrAKI causes

	Pre twenty weeks gestation		Post twenty weeks gestation	
Pre-renal	Sepsis	Urosepsis **Septic abortion** Pneumonia	Sepsis	Urosepsis Pneumonia
	Hypovolaemia	Diarrhoea **Hyperemesis gravidarum**	Hypovolaemia	Diarrhoea
	Hypotension	Cardiac failure Liver failure	Hypotension	Cardiac failure Liver failure
	Drugs	Diuretic use NSAIDS	Drugs	Diuretic use NSAIDS
Intra-renal	Ischaemia	ATN	Ischaemia	ATN RCN
	Interstitial nephritis		Interstitial nephritis	
	Glomerulopathies	Nephrotic/Nephritic syndromes	Glomerulopathies	Nephrotic/Nephritic syndromes
	Microangiopathies	TTP HUS	Microangiopathies	**Preeclampsia spectrum** **AFLP** TTP HUS
	Drugs	Radiocontrast agents NSAIDS	Drugs	Radiocontrast agents NSAIDS
Post-renal	Obstruction	Nephrolithiasis	Obstruction	Nephrolithiasis **Uterine compression** **Iatrogenic**

Bold indicates disease entities unique to pregnancy. NSAIDs: Non-steroidal anti-inflammatory drugs. ATN: Acute tubular necrosis. RCN: Renal cortical necrosis. AFLP: Acute fatty liver of pregnancy. Adapted from Van Hook, 2014.

(usually considered to be 65mmHg in non-pregnant individuals). This results in renal ischaemia, causing ATN and will lead to a subsequent rise in serum urea and creatinine. Additional causes include drugs such as diuretics which can lead to hypovolaemia and non-steroidal anti-inflammatories, which cause AKI via diverse mechanisms.[19]

Presentation after twenty weeks gestation, the HCP is exposed to a surplus of AKI causes unique to pregnancy, including preeclampsia (PE), acute fatty liver of pregnancy, the microangiopathic haemolytic syndromes (thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, HELLP syndromes (haemolysis, elevated liver enzymes and low platelets)) and renal cortical necrosis.

Preeclampsia

Worldwide, PE is the most common cause of PrAKI.[18] Preeclampsia is the new onset of hypertension in a previously normotensive patient after twenty weeks of gestation, associated with other systemic signs such as proteinuria, central nervous system dysfunction, pulmonary oedema and acute kidney injury. When PE is associated with the HELLP syndrome, the risk of AKI increases markedly and can be severe enough to warrant renal replacement therapy (RRT). In this situation, rapid delivery of the fetus is indicated. Hypertension, diabetes and existing chronic kidney disease (CKD) are risk factors for the development of PE and are independent risk factors for the development of PrAKI.[20] The impact of PE on the pregnant patient extends after delivery. Up to 40% of women with previous PE have persistent proteinuria and women who have had PE have a relative risk of 4.7 of developing end stage renal disease (ESRD) in the future. The risk of ESRD also increases with the number of previous pregnancies complicated by PE.[21,22] It is therefore advisable to screen patients with previous PE for persistent proteinuria and if present, prompt referral to a nephrologist is warranted. While PE is the most common cause of PrAKI, other disorders that should also be considered include acute fatty liver of pregnancy (AFLP), thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), a systemic lupus erythematosus flare, antiphospholipid syndrome and pre-existing renal disease.

Pregnancy related thrombotic micorangiopathies

The pregnancy related thrombotic microangiopathies (TMA), TTP and HUS, are both characterised by fibrin and platelet micro-thrombi deposition in the microvasculature, resulting in mechanical haemolysis and thrombocytopaenia.[23] The presentation of these patients is with anaemia, thrombocytopaenia and evidence of haemolysis. Neurological deficits are noted in a subset of these patients, while in others AKI predominates. Where neurological dysfunction is present with a TMA and AKI is not, this is thought to most commonly represent TTP, while HUS is believed to present with TMA, rarely with neurological fallout and commonly with AKI.[23,24] Additionally, the timing of TTP and HUS differ in pregnancy; TTP occurring during the second and third trimester, while HUS occurs predominantly in the early postnatal period. Thrombotic thrombocytopaenic purpura is caused by a deficiency of ADAMTS13, a metalloproteinase that cleaves multimeric von Willebrand factor. The deficiency is either inherited or acquired due to autoantibodies. Pregnancy is associated with a progressive decline in circulating ADAMTS13 levels, and this may predispose to TTP in the later stages of pregnancy.[1,24]

Haemolytic uraemic syndrome is a poorly understood entity. In pregnancy, HUS is not usually associated with the Shiga toxin, but is an atypical HUS (aHUS) that is associated with dysregulation of the complement system, predominantly the atypical pathway.[1,23] Excessive activation of C3 convertase is thought to cause complement activation, leading to endothelial damage and dysfunction. This results in a prothrombotic state, which may precipitate HUS in a susceptible patient. While pregnancy may be a triggering factor in HUS, delivery is not therapeutic.[23]

Treatment of TTP and aHUS is via plasma exchange (PEX). In TTP, PEX replenishes the ADAMTS13 levels while removing the autoantibodies that inhibit ADAMTS13 activity. In addition, PEX removes the ultralarge von Willebrand factor that initiate haemolysis. This ultimately results in reversal of the haemolytic process and stabilisation of the patient. Additional treatments for TTP include glucocorticoids and infusion of fresh plasma, however these therapies are not as effective as PEX.[25] Similarly, treatment of aHUS involves supportive management and when indicated, PEX. The use of PEX in aHUS removes activated complement with apheresis of the plasma, while replenishing unactivaed complement. Recently, eculizumab (a humanized anti-C5 monoclonal antibody) has been shown to be effective in aHUS refractory to PEX.[26]

Of note, TTP, aHUS and PE/HELLP share a common phenotype with TMA being a presenting finding. This may cloud decision making and lead to confusion when decisive management is needed. It should be noted that generally, TTP and HUS do not present with marked liver dysfunction, but this may not always be overt early in the disease.[1]

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare cause of PrAKI, caused by an inherited disorder in the foetus that results in the accumulation of fetal long-chain 3-hydroxyacyl metabolites. These metabolites cross the placenta, accumulate in the maternal circulation and are deposited in the maternal liver, resulting in AFLP.[27,28] The presentation of AFLP can be remarkably similar to that of HELLP syndrome, making diagnosis difficult. The gold standard of AFLP diagnosis is liver biopsy, but this is generally not practical. The presence of marked liver dysfunction, hypoglycaemia, hepatic encephalopathy and coagulation abnormalities, is suggestive of AFLP. Once AFLP is diagnosed, the foetus should be delivered. Wei et al. reported that where delivery is within one week of AFLP diagnosis, survival is 100%, while if delivery is delayed by two weeks, survival drops to 70%.[28] Acute kidney injury develops in approximately 60% of patients with AFLP. This is thought to be multifactorial and may result from prerenal causes such as hepatorenal syndrome or other intrinsic mechanisms.[1,28]

Renal cortical necrosis

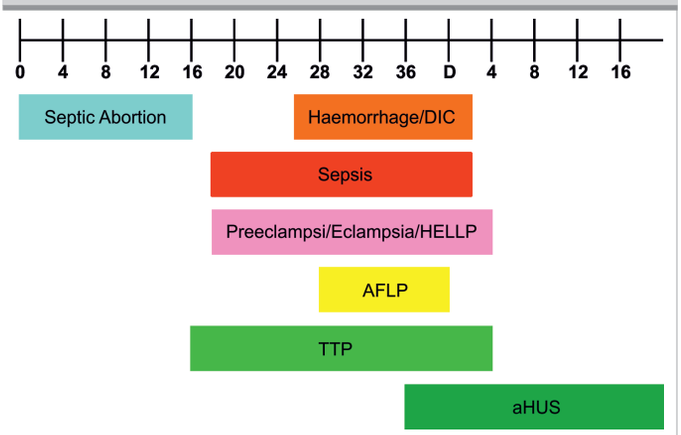
Renal cortical necrosis (RCN) is a consequence of a catastrophic obstetric event, such as massive peripartum haemorrhage, amniotic fluid embolism or disseminated intravascular coagulopathy. The resultant hypotension results in severe renal cortical ischaemia, which results in destruction of the renal cortex in a patchy or diffuse fashion.[29,30] The majority of patients who survive the initial insult and develop RCN will require RRT. As RCN is not reversible, once patients require RRT, the majority with RCN will need lifelong RRT.

Diagnostic approach

Pregnancy related AKI can be masked by the physiological changes in pregnancy, and hence a normal appearing serum creatinine in pregnancy can in actual fact be pathological. This is further confounded when a patient already has underlying CKD; the treating HCP may be unsure if the serum creatinine is normal for the patient or represents a new insult. A serum creatinine value taken before pregnancy or early in the first trimester along with the routine booking bloods would thus be invaluable as a comparison. As this is not routinely performed PrAKI is often missed until the symptoms are profound. This may result in permanent renal injury before clinical interventions are initiated. Additionally, as many of the causes of PrAKI overlap and can be difficult to diagnose, a systematic approach to PrAKI diagnosis is needed. Upon presentation, a thorough history, review of medications (prescription, over the counter and traditional) and examination are essential: the events leading up to presentation and the timing of the AKI relative to the gestation can assist in making the diagnosis.[30] Figure 1 highlights the timing of some common PrAKI entities.

While certain clinical situations will be obvious to the HCW, certain disease entities will have overlapping features. Initial investigations should include a urine dipsticks, microscopic analysis of the urine, a full blood count, liver function test, urea, creatinine and electrolytes, lactate dehydrogenase and a renal ultrasound. Table 5 highlights some of the common abnormalities encountered, while Table 6 highlights some of the characteristics of the different causes of PrAKI.

Figure 1: Relative timing of diseases that cause PrAKI



Numbers indicate weeks of gestation. D: Delivery. DIC: Disseminated intravascular coagulopathy. HELLP: Haemolysis, Elevated Liver enzymes, Low Platelets. AFLP: Acute Fatty Liver of Pregnancy. TTP: Thrombotic Thrombocytopaenic Purpura. aHUS: Atypical Haemolytic Uraemic Syndrome. Adapted from Fakhouri et al. 2012.

Management

Management of PrAKI requires identification of the underlying cause and rapid correction of the insult, as the consequences can be dire to both the mother and the unborn foetus. It is, however, important to recognise that the cause of AKI in pregnancy may be multifactorial, with an underlying disease and concomitant prerenal failure due to other causes such as hypotension, dehydration or haemorrhage.[1] Therefore, prevention of mild PrAKI can often be accomplished by the early recognition of hypovolaemia and the treatment thereof. Nevertheless, a

Table 5: Common investigation abnormalities seen in PrAKI

Test	Abnormality	Possible causes
Urine dipstick	> 1+ Protein Any blood	Glomerular disease Haemorrhage/Haemolysis/Glomerular disease
Urine microscopy	Casts Crenulated red cells Normal red cells	Glomerular disease Glomerular disease Urogenital haemorrhage
Urine protein quantification	> 150mg/24 hours	Glomerular disease
Full blood count	Low haemoglobin Schistocytes/fragments Low platelets	Haemolysis/Haemorrhage Haemolysis Haemolysis/DIC/Sepsis
Liver function test	Raised unconjugated bilirubin Raised ALT/AST	Haemolysis Liver disease (HELLP/AFLP)
Lactate dehydrogenase	Raised	Haemolysis/Liver disease

Table 6: Characteristics of common causes of PrAKI

	BP	GCS	Plt	HB	INR	LDH	AKI	Proteinuria
Sepsis	↓	↔↓	↔↓	↔↓	↑	↑	↑	↔↑
Haemorrhage	↓	↔↓	↑↔↓	↓↓	↔↑	↔	↑	↔
DIC	↓	↔↓	↔↓	↔↓	↔↑	↑	↑	↔↑
PE/HELLP	↑	↓	↓↓	↔↓	↔	↑↑↑	↑↑	↑↑
AFLP	↔↓	↔↓	↓	↔↓	↑↑↑	↑↑↑	↑	↔↑
TTP	↔↓	↓↓	↓↓↓	↓↓	↔	↑↑↑	↑	↑
aHUS	↔↓	↔	↓↓	↓↓	↔	↑↑↑	↑↑↑	↑↑

BP: Blood pressure. GCS: Glasgow coma scale. Plt: Platelets. HB: Haemoglobin. INR: International normalised ratio. LDH: Lactate dehydrogenase. AKI: Acute kidney injury.

judicious approach must be utilised, as a blind protocol driven administration of fluids will undoubtedly lead to fluid overload in the oliguric patient, and hypervolaemia in AKI is associated with an increased mortality.[33] If hypervolaemia is diagnosed in the patient with PrAKI, diuretics should be administered. The aim of diuretics should be to achieve euvolaemia and not to force diuresis. The inappropriate use of diuretics to prevent AKI has been shown to cause hypotension and propagate AKI, leading to progressive decline in renal function and poorer outcomes.[34]

In general, the aim of management of PrAKI should be the maintenance of euvolaemia, restoration of normotension, avoidance of nephrotoxic agents and maintenance of urine output above 0.5 ml/kg/hour. The choice of intravenous fluids is important, with crystalloids being the first fluid of choice.[2] While the use of colloids, such as albumin, is associated with lower volumes infused, there is no difference in outcomes with the use of either saline or albumin in the ICU setting.[31] The exact volume required varies between patients and depends on patient comorbidities and disease aetiology. Instead, endpoints such as mean arterial pressure, urine output, central venous pressure and cardiac output should be monitored.[32]

Additional supportive management such as correction of hyperkalaemia and acidosis must be initiated as soon as these are detected.[1,2] Hyperkalaemia is often asymptomatic in a patient with AKI, but the consequences can be devastating (cardiac arrhythmias, conduction defects, weakness and paralysis) and aggressive management is warranted. If acute measures (glucose and insulin, β adrenergic agonists or sodium bicarbonate) fail, urgent RRT is mandatory, as refractory hyperkalaemia is a life-threatening condition. Similarly, acidosis due to AKI is associated with adverse outcomes (cardiac arrhythmias, depression of cardiac function, immune system dysfunction and generation of a pro-inflammatory state). While life-threatening acidosis should be treated, there is a lack of consensus of when to start therapy with a base, but a pH < 7.1 is considered by some to be an acceptable threshold. It should be noted that correction of acidosis by administration of a base improves neither morbidity nor mortality. This may be due to the fact that administration of base corrects intravenous acidosis, and not cellular acidosis, limiting the overall effect. Additionally, this exposes the patient to the risk of a high sodium load.[35] Again, if acidosis is persistent and does not respond to supportive measures, RRT is indicated.

There are no guidelines on the timing of RRT initiation in AKI, let alone in PrAKI. However, RRT should be considered in all patients with PrAKI when there are life-threatening indications, such as fluid overload, acid-base and electrolyte abnormalities or oliguria. Renal replacement therapy tends to be avoided when the nephrologist suspects the patient may recover renal function, as RRT is not benign, and may paradoxically worsen AKI via mechanisms such as hypovolaemia. The goals of RRT in AKI are to maintain euvolaemia, electrolyte homeostasis and remove metabolic waste products, while allowing for renal recovery, thus temporising the patient while awaiting other therapeutic measures.[2] Renal replacement therapy is not a definitive treatment for PrAKI, but rather a supportive tool that bridges the patient while a definitive treatment is sought.

In summary, PrAKI is a silent and often overlooked syndrome, which is associated with dire consequences for both the mother and the foetus. The long term risk to the mother for recurrent PrAKI, PE and ESRD requiring RRT after just one occurrence of PrAKI are high. In South Africa, this impact is often overlooked, much to the detriment of the mother. Once PrAKI has been diagnosed and managed, the postpartum management of such a patient should include a screening urea and creatinine, along with a urinary dipstick analysis. If any abnormality is detected, prompt referral to a nephrologist is warranted for further management of ongoing renal disease due to, or worsened by the PrAKI.

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