Best Practice & Research Clinical Obstetrics and Gynaecology 57 (2019) 47–59

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

4

Acute kidney injury in pregnancy including renal disease diagnosed in pregnancy

David R. Hall, Maternal-Fetal Medicine Sub-specialist [a, *], Frances Conti-Ramsden, Academic Clinical Fellow in Obstetrics & Gynaecology [b]

[a] Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa
[b] Department of Women and Children's Health, King's College London, London, UK

Keywords:
Pregnancy
Acute kidney injury
Pre-eclampsia

A B S T R A C T

Pregnancy-related acute kidney injury (AKI) is a rare but serious complication in high-income settings and remains an important cause of maternal and foetal morbidity and mortality in low- and middle-income settings. Hypertensive disorders of pregnancy are the leading cause of pregnancy-related AKI worldwide. In this article, we outline the epidemiology, aetiology, recognition, investigation and management of pregnancy-related AKI. Difficulties in the definition of AKI, approaches to determine the cause of AKI in diagnostically challenging circumstances and diagnosis of new renal disease in pregnancy are discussed.

Introduction

Acute kidney injury (AKI) is estimated to affect between 9% and 20% of hospitalised patients [1,2] and more than 50% of intensive care patients [3] despite a significant proportion of cases being preventable. It carries a significant burden of morbidity and mortality [4] and is an independent risk factor for all-cause mortality, cardiovascular disease and development of chronic kidney disease (CKD) and end-stage renal failure [5,6]. The global incidence of AKI in pregnancy has generally declined due to

* Corresponding author. Department of Obstetrics and Gynaecology, PO Box 241, Cape Town, 8000, South Africa.
E-mail address: drh@sun.ac.za (D.R. Hall).

https://doi.org/10.1016/j.bpobgyn.2018.12.005
1521-6934/

improvements in the quality of reproductive healthcare, particularly access to abortion services and improvements in antenatal and peripartum care [7–9]. However, in low- and middle-income countries (LMICs), it is still an important contributor to maternal morbidity and mortality and remains a common reason for requiring dialysis [8,10]. Whilst in high-income countries (HICs) AKI in pregnancy is rare, recent US data have demonstrated an almost threefold increase in rates during a 10-year period [11]. The prompt identification, appropriate management and follow-up of AKI in pregnancy therefore remain an important subject for obstetricians, obstetric physicians, nephrologists and critical care providers in both HIC and LMIC settings.

Epidemiology

The International Society of Nephrology estimates that AKI occurs in approximately 13.3 million people per year across the globe, with more than 85% living in LMICs [12]. In 2016, the International Society of Nephrology reported the 'Zero by 25' Global Snapshot on recognition and management of AKI. This 'snapshot' came from prospective paediatric and adult data collected from 289 centres in 72 countries. Overall, 1% of AKI was pregnancy related; however, the burden was highest in low- and lower-middle-income countries (LLMIC) where 3.1% cases of AKI were pregnancy related compared to 0.3% of cases in HICs [13]. Numerous studies investigating aetiology suggest that hypertensive disorders of pregnancy are the most common cause of AKI in pregnancy [10,14,15].

In HICs, the incidence of pregnancy-related AKI has remarkably reduced from approximately 1/300 to 1/15,000–1/20,000 pregnancies from the 1960s–1990s [9,16]. Legalisation of abortion and improvements in quality of and access to antenatal care are thought to be the main drivers underlying this trend [7,17]. However, more recent data from Canada and the US show pregnancy-related AKI to be increasing. In Canada, rates have increased from 1.6 to 2.3 per 10,000 deliveries between 2003 and 2007 [18], and in the US from 2.3 to 4.5 per 10,000 deliveries between 1998 and 2008 [11]. These findings are concerning given the association with maternal morbidity and mortality, with recent Canadian data showing a case-fatality rate of 2.9% [19]. These trends may be explained by increasing levels of obesity, comorbid conditions such as hypertension and diabetes and increasing maternal age as women delay first pregnancy, which in turn are risk factors for obstetric complications. However, changes in the management of obstetric conditions could also be implicated. In one retrospective cohort study, the increase in pregnancy-related AKI was only observed in women with hypertensive disorders of pregnancy, and the authors discussed whether emphasis on fluid restriction in managing these women in the last decades could be an aetiological factor [20].

In LMICs, the true burden of pregnancy-related AKI is difficult to estimate. There is a bimodal distribution with a first peak between 8 and 16 weeks of gestation in association with septic abortions and a late peak closer to term (34–36 weeks) associated with complications such as pre-eclampsia, placental abruption, haemorrhage and sepsis [10]. Several studies have found evidence of decline in pregnancy-related AKI in middle-income settings, for example, between 4% and 7% cases of AKI in India are currently estimated to be pregnancy related compared to 17%–43% of cases in the 1960s [21,22]. Similar to high-income settings, this improvement is attributed to the legalisation of pregnancy termination and improvements in antenatal care. However, a considerable burden remains; a recent study of pregnancy-related AKI in the third trimester from the Indian subcontinent reported 178 cases of AKI per 10,000 deliveries representing approximately 20% of all cases of AKI. Pre-eclampsia was the most common cause (35%) followed by puerperal sepsis (25%). Associated rates of neonatal and maternal mortality were high (39% and 20%, respectively) [10]. Another centre reported 60% of cases of pregnancy-related AKI requiring dialysis and a mortality rate of 20% [22]. Differences in definitions of pregnancy-related AKI, as well as regional and national differences in general population health and healthcare, are likely to contribute to variability in the incidence and reported outcomes between studies.

Renal physiology in pregnancy

Significant changes in kidney function relevant to the diagnosis of AKI occur in normal pregnancy. The kidney and renal pelvis enlarge, while there is dilatation and relative obstruction of the ureters

together with associated stasis or reflux. Early in pregnancy, peripheral vascular resistance reduces, thus driving an increase in cardiac output (by approximately 50% above the baseline) and plasma volume (by approximately 40% above the baseline), and lowering of blood pressure. Red cell mass also increases but not as substantially as plasma volume, thus leading to a mild relative anaemia in pregnancy. Volume expansion in combination with increased cardiac output causes an increase in renal plasma flow early in pregnancy, which is increased by 50%–85% by 16 weeks of gestation. This drives hyperfiltration, thereby increasing the glomerular filtration rate (GFR) by 40%–65% from the baseline, thereby resulting in lower serum urea and creatinine levels [23,24]. Protein excretion also increases progressively during pregnancy (<300 mg/24 h being normal), which is attributed to the increase in GFR, alterations in the glomerular basement membrane and reduced proximal tubular reabsorption [17,23]. Knowledge of these functional changes is important, as serum creatinine and urea values considered normal in non-pregnant women may reflect a decrease in renal function for the pregnant patient, and increasing proteinuria in women with chronic renal disease does not necessarily signify deterioration.

Defining AKI in pregnancy

AKI is characterised by a rapid decrease in renal function over hours or days, thereby resulting in an increase in metabolic waste products. Apart from increasing serum creatinine and urea levels, a decrease in urine output may also be detected. An accepted definition of AKI during pregnancy is challenging in view of the physiological changes in GFR during pregnancy, normal gestational changes in serum creatinine and lack of baseline creatinine in almost all pregnant women apart from those with CKD. The equations used to calculate GFR are inaccurate in pregnancy, with the Modification of Diet in Renal Disease (MDRD) shown to underestimate, and the Cockcroft-Gault formula overestimate, the true GFR value, leaving 24-h urinary creatinine clearance as the gold standard method [25,26]. In addition, gestation and ethnicity-specific creatinine normal ranges for pregnancy have not been standardised or validated. As such, the international definitions of AKI outside of pregnancy are not validated for use in pregnancy, and there is potential for pregnant women with AKI to have creatinine levels falling within the 'normal range' for non-pregnant women despite a significant fall in GFR. The uncertainty regarding definition is illustrated in the variation in diagnostic criteria in the literature to date, with a recent systematic review and meta-analysis of pregnancy outcomes in AKI reporting studies using varying definitions of AKI including the RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease) classification, AKIN (Acute Kidney Injury Network) definition, absolute serum creatinine cut-offs and oliguria [27].

Whilst a validated definition of AKI in pregnancy remains lacking and an important topic of research, we propose the KDIGO (Kidney Disease: Improving Global Outcomes) definition of AKI [28], which has merged RIFLE and AKIN criteria, been validated outside of pregnancy and has gained international consensus as a useful guideline [29]. The KDIGO diagnostic criteria are shown in Table 1. It should be noted that these are non-pregnant AKI definitions. Where baseline creatinine values are

Table 1
KDIGO definition of AKI for adults and children. From: Kidney Disease: Improving Global Outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney international, Suppl. 2012; 2: 1–138 [28].

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patient < 18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥ 12 h

known, AKI can be diagnosed by an increase in creatinine greater than 1.5-fold above the baseline or an absolute increase of greater than 26 μmol/L. However, it is common in both high- and low- and middle-income settings that women may have their renal function tested for the first time when they are unwell in pregnancy. Where no baseline exists, individual creatinine values need careful interpretation, with monitoring of the trend in renal function being most informative, and the possibility of underlying CKD also being considered.

Similarly, oliguria as outlined in the KDIGO criteria may also indicate developing AKI. However, it is important to be aware that under certain conditions of pregnancy such as pre-eclampsia, oliguria is often observed as a normal renal response to intravascular depletion, as well as several conditions not specific to pregnancy such as pain and the post-operative phase. Conversely, anuria is never normal and should be treated as an emergency. It is prudent to use early markers such as increasing or a high creatinine level and oliguria rather than serious end points such as requirement for dialysis to identify patients early when the condition is potentially reversible.

Aetiology

AKI in pregnancy most often occurs in women with previously healthy kidneys but may also complicate the course of pregnancy in women with known or unknown pre-existing renal disease. The latter may be particularly true in settings where provision or the utilisation of healthcare services are sub-optimal, and therefore, chronic renal disease may be diagnosed for the first time in pregnancy. New renal disease may also develop or be unmasked during pregnancy. Therefore, whilst pregnancy-specific conditions are responsible for most cases of AKI, clinicians must consider a wide differential diagnosis including renal conditions that affect women of reproductive age.

Causes of AKI

As in non-pregnant patients, the causes of AKI can be divided into three groups: pre-renal, renal and post-renal or obstructive causes. In addition, causes can be pragmatically divided into whether they occur early or late in gestation. The majority of cases of pregnancy-related AKI will have an underlying obstetric cause. These causes are summarised in Table 2. However, renal causes, although rarer, must also be considered. The differential diagnosis of intrinsic renal disease in women of reproductive age is summarised in Table 3. These diseases may present at any gestational week in pregnancy.

In the pre-renal category, decreased renal perfusion due to absolute or relative hypovolaemia is the underlying pathology. However, if untreated, pre-renal AKI can lead to acute tubular injury, thereby causing intrinsic renal damage. Obstetric haemorrhage and sepsis, including puerperal sepsis and pyelonephritis, are common causes of pre-renal AKI. In addition, sepsis is increasingly recognised to have direct nephrotoxic effects. Renal causes have specific effects on renal parenchyma and are

Table 2
Pregnancy-related causes of AKI. HELLP = Haemolysis, elevated liver enzymes and low platelet syndrome.

	Early causes	Late causes
Pre-renal	Haemorrhage (abortion, ectopic pregnancy)	Obstetric haemorrhage: antepartum (placenta praevia, placental abruption, placenta accreta), post-partum (atony, trauma, uterine rupture)
	Sepsis and septic shock (abortion, retained products of conception, pyelonephritis) Hyperemesis gravidarum	Sepsis (pyelonephritis, chorioamnionitis, puerperal sepsis)
Renal		Pre-eclampsia HELLP syndrome Acute fatty liver of pregnancy Thrombotic thrombocytopenic purpura (TTP) Atypical haemolytic uraemic syndrome (aHUS)
Post-renal		Obstruction (gravid uterus, masses, e.g. cervical cancer, renal stones) Surgery (ureter damage)

Table 3
Differential diagnosis of intrinsic renal disease in women of reproductive age. NSAID = Non-steroidal anti-inflammatory drug. ANCA = Anti-neutrophil cytoplasmic antibodies.

Pathophysiology	Diagnoses
Tubular necrosis (prolonged pre-renal ischaemia or nephrotoxins)	Prolonged ischaemia (any cause of hypotension, hypovolaemia) Drugs and toxins (NSAIDs, aminoglycosides, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, radiocontrast media)
Vascular disease including vasculitis	Takayasu's arteritis, ANCA vasculitides: granulomatosis with polyangiitis.
Glomerular disease (may present as nephrotic syndrome)	Lupus nephritis, diabetic nephropathy, primary and secondary focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, IgA nephropathy, thin basement membrane disease, mesangial proliferative glomerulonephritis, HIV-associated nephropathy, post-infectious glomerulonephritis, rapidly progressive glomerulonephritis, fibrillary glomerulonephritis.
Acute interstitial nephritis (hypersensitivity response)	Drugs (NSAIDs, penicillins, cephalosporins, thiazide diuretics, furosemide, phenytoin, allopurinol), infiltrative disease, e.g. sarcoidosis, infectious disease, e.g. Legionnaires disease, autoimmune diseases.
Structural	Single kidneys, other structural abnormalities.

primarily toxin or immune mediated. This category includes causes such as the microangiopathy associated with pre-eclampsia; haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome (aHUS), as well as infective or immune-mediated glomerulonephritis and other renal conditions. Pre-eclampsia, acute fatty liver of pregnancy, certain medications and pre-renal causes may also give rise to acute tubular injury. In the post-renal category obstruction of the urethra or ureters by the gravid uterus (particularly in cases of multiple pregnancies or polyhydramnios), kidney stones or extrinsic compression are rare causes. In general terms, the pre-renal causes are more common at earlier gestations due to septic abortion and hyperemesis gravidarum, whilst in later pregnancy, renal causes associated with obstetric complications such as pre-eclampsia, HELLP and thrombotic microangiopathies are more common.

Pathophysiology

The clinician should understand the effect of the clinical picture on the pathology occurring within the kidney. When considering a pre-renal (ischaemic) insult to the kidney, there are largely three conditions that represent a continuum of increasing severity within the common pathological process. Early AKI results from moderate renal ischaemia and is usually a mild form of disease that is reversible if renal perfusion is restored. This may progress to acute tubular injury, which follows more prolonged ischaemia, but is also reversible as the damage is limited to metabolically active tubular cells. The final stage, renal cortical necrosis (RCN), follows severe renal ischaemia with disintegration of both glomeruli and tubules in the renal cortex. Although this is irreversible, the regional involvement is often incomplete or 'patchy,' thereby allowing a degree of recovery. In developing countries, obstetric complications such as septic abortion, placental abruption and disseminated intravascular coagulation are the main causes of RCN, but reassuringly, the incidence of RCN in pregnancy-related AKI cases decreased from 4.7% of cases between 1984 and 1994 to 0.5% between 1995 and 2005 in a longitudinal study from India [30].

The above three conditions can usually be recognised in clinical phases of AKI, beginning with oliguria as noted in the definitions. At this stage, it is not possible to distinguish tubular from cortical necrosis. When anuria is present, obstruction should always be excluded. Following the oliguria, a phase of polyuria with markedly increased urine output may ensue, lasting from days to weeks. In this phase, serum urea and creatinine levels may continue to increase. With the passage of large volumes of urine, careful attention must be given to fluid and electrolyte replacement. Thereafter, urine levels revert to more normal volumes, with complete or variable return of kidney function. Ultimately, the obstetrician has an advantage in that most pregnant women who experience AKI are young with previously healthy kidneys, but the long-term consequences remain unknown.

Diagnosis and investigation

Every patient at risk of or presenting with pregnancy-related AKI who is clinically stable should have a detailed history, physical examination and laboratory investigations that a diagnosis be made, including exclusion of systemic disease. In unstable patients, resuscitation should be delivered. Examination should include determination of vital signs including heart rate, blood pressure and an assessment of fluid balance. Insertion of an indwelling bladder catheter is strongly recommended, as careful monitoring of fluid input and output is required (normal urine output is approximately 0.5 ml/kg/h). Serum urea, creatinine and electrolytes; full blood count and liver function tests should be evaluated. Urine dipstick should be performed before catheterisation for blood, protein, leucocytes, nitrites and glucose and sent for microscopy and culture if appropriate. Proteinuria should be confirmed through quantification either by protein creatinine ratio (PCR) testing or 24-h urinary protein collection. Renal ultrasound is an important tool to exclude obstruction as a cause, although the high incidence of physiological hydronephrosis during pregnancy, generally more prominent on the right than the left side and not severe, must be remembered. Renal size is a useful additional measure as bilateral small kidneys may be indicative of underlying CKD. In most cases, the aetiology of pregnancy-related AKI will be apparent after an appropriate history, physical examination and basic bedside and biochemical tests, with pre-eclampsia, obstetric haemorrhage and sepsis featuring prominently.

In cases where the diagnosis is not apparent after an initial assessment, renal pathologies can be distinguished by abnormal urinary sediment such as red blood cell casts. Diagnostic difficulties in determining the underlying aetiology of pregnancy-related AKI most often arise in the renal category, particularly in the differentiation of pre-eclampsia (the most likely diagnosis) from rarer causes, which also can present with proteinuria, renal impairment and varying degrees of hypertension such as de novo renal disease, acute fatty liver of pregnancy (AFLP), and the thrombotic microangiopathies (TMAs). An overview of distinguishing features of conditions that can imitate each other alongside key management principles is shown in Table 4, and general investigation and management principles are shown in Fig. 1.

The role of renal biopsy

Renal biopsy is almost never necessary for AKI in pregnancy. In most cases, an appropriate history, examination and special investigations reveal the diagnosis. For this reason, renal biopsy is reserved for severe pregnancy-related AKI without other clinical clues, an anticipated diagnosis with established therapy or when prolongation of pregnancy is a priority, such as in the second trimester. The risk of

Table 4
Differentiating pre-eclampsia/HELLP, thrombotic thrombocytopenic purpura (TTP), atypical haemolytic uraemic syndrome (aHUS) and acute fatty liver of pregnancy (AFLP) and key management principles. HELLP = haemolysis, elevated liver enzymes and low platelets. vWF = von Willebrand factor.

	Pre-eclampsia/HELLP	TTP	aHUS	AFLP
Onset	Usually third trimester	Second or third trimester	Mostly post-partum	Mostly around term
Key clinical features	Hypertension and proteinuria	Neurologic symptoms, fever and purpura	Severe kidney injury	Nausea, vomiting and malaise
Key laboratory features	Thrombocytopenia, mild haemolysis and increase in liver transaminases	Severe haemolysis and thrombocytopenia; vWf multimers present; severely decreased ADAMTS13 activity (<10%)	Severe haemolysis, thrombocytopenia	Hypoglycaemia, coagulopathy (increase in INR) and increase in liver transaminases
Renal injury	Mild/moderate	Mild/moderate	Severe	Moderate
Renal recovery after delivery	Good, recovery within days to week of delivery.	Poor, low chance of renal recovery.	Poor, low chance of renal recovery.	Good, recovery within days of delivery.
Key treatment principles	Delivery, control of hypertension	Plasma exchange	Plasma exchange, complement pathway inhibition with eculizumab	Delivery, supportive measures

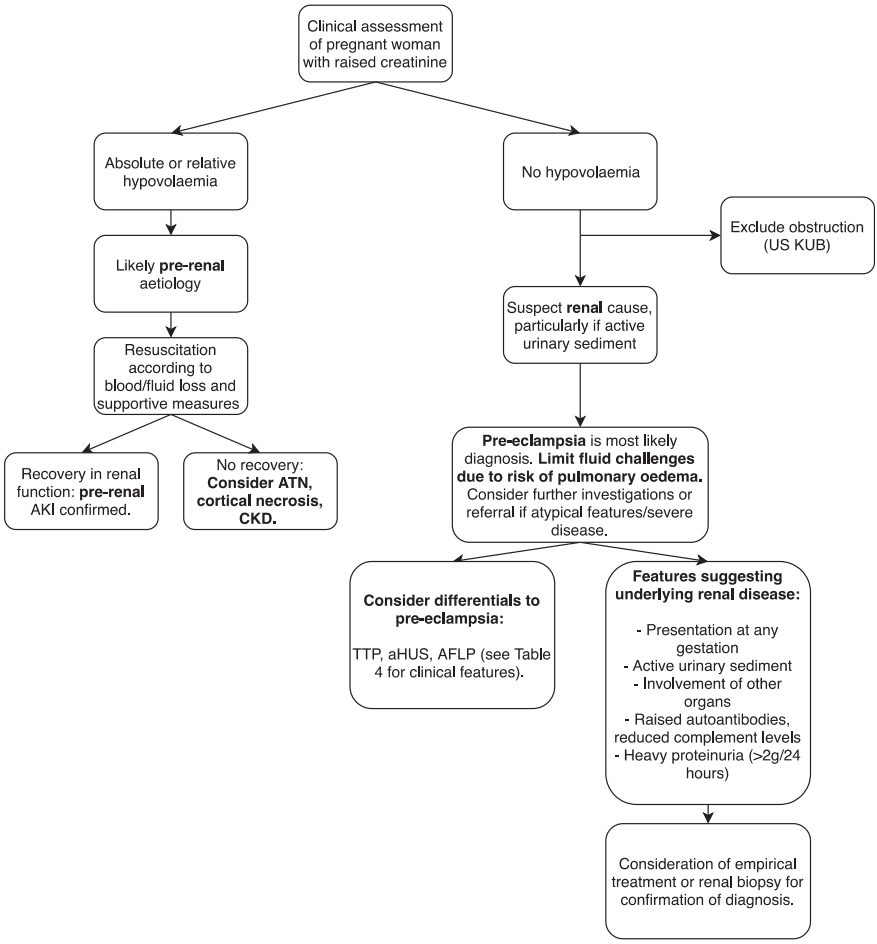

Fig. 1. Approach to acute kidney injury in pregnancy. TTP = thrombotic thrombocytopenic purpura, aHUS = atypical haemolytic uraemic syndrome, AFLP = acute fatty liver of pregnancy.

complications following renal biopsy in pregnancy is 7% compared to that of 1% after delivery according to a recent systematic review, with a 2% risk of major bleeding in pregnancy, particularly for renal biopsies performed in the second trimester [31]. Therefore renal biopsy is only indicated where the results might change management during pregnancy, such as where heavy proteinuria is present with a rapid decrease in glomerular filtration rate, particularly in preterm pregnancy. Finding histology suggestive of diseases other than pre-eclampsia may therefore identify patients who can be managed without delivery. In these cases, a renal physician should be consulted and the biopsy result should be interpreted by a renal pathologist familiar with changes during pregnancy. In most clinical scenarios, delivery will first be accomplished and biopsy delayed.

Management

Managing women with pregnancy-related AKI is challenging, requiring consideration of mother and foetus. In severe cases, multidisciplinary input may be required from obstetricians, maternal medicine specialists, haematologists, nephrologists, neonatologists and critical care specialists. Management can be divided into prevention of further damage by general supportive measures, management of complications of acute renal failure including dialysis and treatment of the underlying cause.

General supportive measures

The central principle of management is to provide symptomatic and supportive care until renal function returns, with various levels of monitoring according to the level of care required. Patients not responding to initial simple conservative measures at lower levels of care must be discussed with and, if necessary, referred to a specialist centre without delay. Upon diagnosis of AKI, a careful medication review must be undertaken and any drugs with potential to cause further renal damage stopped if possible (commonly non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics and radiocontrast agents). Renal clearance medications may also need dose adjustment according to the degree of renal impairment, with a prominent example being maintenance doses of magnesium sulphate, which is utilised in the management of severe pre-eclampsia and eclampsia. The loading dose of magnesium sulphate is safe, even in renal shut-down.

Fluid balance management

The most important aspect of supportive management is fluid management, with the aim of restoring and maintaining renal perfusion and limiting further damage. The initial steps should address causative factors such as sepsis, replacement of blood and fluid losses and adequately maintain blood pressure levels to ensure sufficient renal perfusion. Careful attention must be paid to fluid balance in pregnant patients, as excessive fluid transfusion in patients with oliguria may result in fluid overload, thereby causing serious iatrogenic problems. As it can be challenging to assess the intravascular volume in a pregnant or postpartum woman by physical examination alone, in more serious cases, a central venous pressure (CVP) line (separate from an intravenous therapy infusion line), arterial line, echocardiography and, occasionally, a pulmonary artery catheter are considered.

The clinician must carefully distinguish between renal insufficiency caused by hypovolaemia or hypotension and cases where acute tubular injury or cortical necrosis is present, as the therapy for these conditions differs greatly. When oliguria results from clinical hypovolaemia, resuscitation should be performed according to blood or fluid loss and blood pressure, heart rate and, if necessary, serial CVP values measured to ascertain return to normal levels. However, the administration of large amounts of fluid where acute tubular injury or cortical necrosis is likely is potentially harmful because of the risk of fluid overload. Therefore, when oliguria is present with uncertain volume status against the background of a condition such as severe pre-eclampsia, the initial fluid replacement should be restricted to a small 250 ml crystalloid fluid challenge after ensuring that no pulmonary congestion is present. This could be repeated once. If there is no further response in uncertain cases, or when severe pre-eclampsia is present, these cases should be referred to specialist centres with the necessary expertise for closer assessment of the volume status. Potassium-containing fluids should be avoided for resuscitation.

When the diagnosis of acute tubular injury is made (persistent oliguria with increasing serum, urea and creatinine levels), fluid restriction and careful biochemical monitoring must be instituted. The diet should avoid potassium and phosphate and provide high-quality but not excessive protein. Inadequate intake of calories promotes catabolism. Volume balance may be achieved by administering the equivalent of total urinary output during the preceding 24 h together with 500 ml of fluid in an adult non-febrile woman. Overhydration is the danger during this stage. Serum potassium levels should be carefully checked due to the dangers of hyperkalaemia and attention should also be given to the acid–base balance due to the danger of metabolic acidosis. By contrast, careful supervision and electrolyte replacement are important in the polyuric phase. After commencement of sustained diuresis, central monitoring may be discontinued and electrolyte levels should be monitored until they have returned to normal. These patients are most often managed in a multidisciplinary setting with the input of nephrologists and intensivists.

Pharmacological therapies

Loop diuretics have been commonly used in the management of AKI worldwide, with the rationale that converting oliguric to non-oliguric AKI is advantageous, as prognostically non-oliguric renal failure is more favourable with less requirement for dialysis. Although the administration of furosemide in cases with oliguria is a common practice, there is no evidence of the beneficial effect of diuretics on

renal prognosis. Observational cohort data suggest increased mortality and poorer renal outcomes with diuretic use in critically ill patients with AKI [32], and a large multicentre prospective cohort study demonstrated no difference in mortality rates [33]. When used early (within the first 48 h), diuretics in the management of patients with AKI are rarely harmful and may assist in fluid management in cases of volume overload if certain simple precautions are taken. Diuretics must be avoided in patients with pre-eclampsia unless pulmonary oedema is present, or CVP monitoring reveals sufficient intravascular volume expansion. Repeated high doses of furosemide may cause ototoxicity. This danger may be minimised by limiting the rate of infusion below 15 mg/min and adhering to current practice favouring lower doses [34].

Low-dose dopamine infusion has historically been used for the prevention and treatment of AKI due to it increasing renal perfusion through a vasodilatory effect on the renal arterioles. However, both a systematic review and a meta-analysis showed no benefit on renal function in acute renal failure or reduction in need for dialysis outside of pregnancy [35,36], and no evidence of benefit has been found in a limited review of the use of low-dose dopamine in severe pre-eclampsia [37]. Given the substantial side effects of dopamine including tachyarrhythmias, gastrointestinal or digital necrosis and concerns on potential impact on uterine blood flow, there appears to be little role of this agent in the management of AKI in pregnancy.

Management of complications of renal failure and dialysis

The common complications of renal failure including hyperkalaemia, metabolic acidosis and anaemia must be monitored for and may require treatment short of dialysis. Patients with hyperkalaemia should have an ECG and treatment administered if there is evidence of ECG changes or a serum potassium level of 6 mmol/L or more. Cardioprotection should be administered urgently in the form of a calcium salt (calcium gluconate or calcium chloride), and potassium should be driven into the intracellular compartment through the use of an insulin with glucose infusion (commonly 10 units actrapid in 25 g glucose solution), with 10–20 mg of nebulised salbutamol being an adjunct treatment. Metabolic acidosis can be managed with intravenous sodium bicarbonate (or oral administration if fluid overloaded), and anaemia may require transfusion in the acute setting or erythropoietin therapy may need to be considered in prolonged cases.

Renal replacement therapy

In most cases, AKI will respond to supportive measures, but when this approach is unsuccessful or patients present late in the course of their illness, dialysis may be necessary. Haemodialysis and peritoneal dialysis have both been described in pregnant and recently delivered women, but mostly dialysis is initiated post-partum given the major causes of AKI in pregnancy. The main indications for dialysis are volume overload, refractory hyperkalaemia or metabolic acidosis, or severe uraemic symptoms (pericarditis, neuropathy or encephalopathy). Although such cases are rare in developed countries, this is different in LMICs where sepsis, pre-eclampsia and obstetric haemorrhage remain problematic. In a small study from South Africa, the percentage of pregnant women with AKI requiring dialysis was approximately 10% [38], but these cases were not followed up long term. Studies of pregnancy-related AKI from the Indian subcontinent have reported rates of dialysis as high as 50% [21].

The threshold for the initiation of dialysis in pregnancy requires consideration of the impact of renal failure on the foetus and uteroplacental blood flow, and early initiation of renal replacement therapy may be of benefit, but as yet little evidence exists to guide clinical decision-making. The literature on renal replacement in pregnancy is primarily on women with CKD and therefore requires extrapolation to pregnancy-related AKI. There is adequate evidence that an increased dialysis dose (daily dialysis for >20 h/week) should be the standard of care in pregnancy and is associated with improved foetal outcomes [39], which is likely to be due to reduction in prematurity and polyhydramnios from reduction in uraemia. Whilst most data relate to intermittent haemodialysis, continuous renal replacement therapy (CRRT) in the critical care setting may have the advantage of continuous control of volume and avoid haemodynamic instability inherent to intermittent haemodialysis, which may be beneficial in pregnancy but requires further investigation.

Treatment of the underlying cause

When pregnancy-related AKI occurs, the aetiology must be determined and, if possible, reversed. The clinician must also determine the appropriate level of care according to the underlying diagnosis and severity of AKI and, if necessary, refer. If still undelivered, consideration of the route and timing of delivery is required.

In cases of pre-renal failure such as observed in haemorrhage and sepsis, timely correction of renal perfusion by resuscitation with fluid and/or blood products is crucial to prevent the transition from a pre-renal insult to one causing intrinsic renal and potential long-term damage. Delivery may be necessary as part of resuscitation and stabilisation, for example, to control bleeding or to remove the source of sepsis in suspected chorioamnionitis. In cases of post-renal failure, relieving obstruction is the priority and may need discussion with urologists, with consideration of ureteric stenting or nephrostomies as appropriate.

When considering renal causes of pregnancy-related AKI, it is of critical importance to determine the underlying pathology so that an appropriate decision can be made regarding delivery and appropriate management, which varies significantly. Hypertension must be carefully managed with appropriate agents [40]. In cases of pre-eclampsia, placental abruption, HELLP syndrome and possibly acute fatty liver of pregnancy, prompt delivery is the only 'cure' and in addition to adequate supportive measures may reverse the maternal organ dysfunction. However, TMAs and intrinsic renal disorders such as lupus nephritis do not necessarily warrant delivery. Renal biopsy may need to be considered in these complex cases to confirm the diagnosis and guide management, as well as avoid potential iatrogenic preterm delivery. Thrombotic microangiopathies should be treated with plasma exchange in cases of TTP [41], and improved outcomes have been demonstrated using eculizumab for complement pathway inhibition in aHUS [42]. Glomerulonephritis flares are often treated with steroids and other immunosuppressants deemed safe in pregnancy. Finally, the management of acute tubular injury is supportive, with restoration of intravascular volume, avoidance of nephrotoxins and support in the form of dialysis as required.

Outcomes

Data from single-centre studies suggests that pregnancy-related AKI is associated with high rates of foetal and maternal morbidity and mortality. However, accurate estimation of these risks has been limited by the lack of consensus on the definition of AKI in pregnancy, small sample size and retrospective nature of many studies. A recent systematic review and meta-analysis of maternal and foetal outcomes of pregnancy-related AKI including almost 6000 pregnancies in 11 studies from a variety of settings (data from China, France, Tunisia, Morocco and Turkey) has confirmed that pregnancy-related AKI is associated with a higher risk of maternal death (odds ratio 4.5), stillbirth and perinatal death (odds ratio 3.39), longer intensive care unit stays (weighted mean difference 2.13 days), lower baby birthweight (weighted mean difference −740 g), lower gestational age at delivery (weighted mean difference −0.7 weeks) and delivery by caesarean section (odds ratio 1.49) [27]. It must be noted that the definitions of pregnancy-related AKI in the included studies varied considerably. The high rate of maternal mortality (13.3%) in the study is in keeping with other studies from LMIC settings [43,44].

In terms of renal outcomes, previously AKI was thought to be an entirely reversible syndrome. However, there is mounting evidence outside of pregnancy that AKI leads to an increased risk of CKD [5,6]. There are limited data available relating to pregnancy-related AKI, but in the majority of cases, AKI appears to be reversible, with rates of renal recovery reported between 60% and 90% in HIC settings [8,45]. However, the underlying aetiology is an important factor, with high rates of renal insufficiency and requirement of dialysis and transplantation following pregnancy-related TMA in one study [46].

Follow-up of women who have an episode of pregnancy-related AKI is also of importance, particularly those with a renal aetiology such as pre-eclampsia. At 6 months post-partum, proteinuria secondary to pre-eclampsia will have resolved in more than 95% of women [47]. Therefore, women with persistent post-partum proteinuria following an episode of pre-eclampsia warrant referral to

nephrology, and indeed, high rates of underlying renal disease (greater than 70%) have been found in women biopsied for persistent postpartum proteinuria [48]. The 6-week postnatal check offers adequate opportunity for follow-up of these women, with dipstick testing of urine for proteinuria and repeat renal function if recovery was incomplete at discharge, and onward referral as necessary.

Summary

AKI in pregnancy remains an important contributor to maternal morbidity and mortality, worldwide. Increasing levels of obesity, hypertension and diabetes exacerbate the problem. AKI may occur in women with previously healthy kidneys and can also complicate the course of pregnancy in women with known pre-existing renal disease. In addition, where provision or the utilisation of healthcare services are sub-optimal, chronic renal disease may be diagnosed for the first time in pregnancy. Although AKI is characterised by a rapid decrease in renal function for hours or days resulting in an increase in metabolic waste products, a generally accepted definition of AKI during pregnancy is challenging. As in non-pregnant patients, the causes of AKI are divided into three groups: pre-renal, renal and post-renal or obstructive causes, but causes can also be pragmatically divided into whether they occur early or late in gestation. The majority of cases of pregnancy-related AKI will have an underlying obstetric cause with pre-eclampsia, obstetric haemorrhage (especially placental abruption and post-partum haemorrhage) and septic shock, of particular importance. After diagnosis, the management is directed towards prevention of further damage by general supportive measures, management of hypertension, management of complications of acute renal failure including dialysis and treatment of the underlying cause. In the majority of cases, AKI is reversible, but it is important to identify cases with incomplete recovery. The six-week postnatal check offers adequate opportunity for follow-up of these women, with onward referral as necessary. The long-term implications of AKI in pregnancy are unknown.

Practice points

- All women presenting with or at risk of pregnancy-related AKI should have a full history, examination and basic bedside and blood investigations to identify pregnancy complications, e.g. pre-eclampsia, or underlying disease, e.g. systemic lupus erythematosus.
- Pre-renal causes of AKI (most commonly, haemorrhage and sepsis) should be managed with appropriate volume replacement and maintenance of blood pressure.
- Renal causes of AKI need careful workup to distinguish pre-eclampsia and HELLP from AFLP, intrinsic renal disease and TMAs.
- Women with AKI in pregnancy should be followed up at the 6-week postnatal visit to check for persistent proteinuria or renal impairment. If present, these may warrant referral to nephrology services.

Research agenda

- Development and validation of sensitive and specific diagnostic criteria for AKI in pregnancy, including gestation-specific creatinine reference ranges.
- Investigation of whether novel plasma or urinary biomarkers have utility in the early identification of AKI in pregnancy.
- Investigation of the impact of mode and delivery of renal replacement therapy on maternal and foetal outcomes of AKI in pregnancy.
- Investigation of the long-term renal outcomes of AKI in pregnancy with regard to recurrent AKI or CKD.

Conflicts of interest

None.

Acknowledgements

No funding was received in relation to this article.

References

[1] Bedford M, Stevens PE, Wheeler TWK, Farmer CKT. What is the real impact of acute kidney injury? BMC Nephrol 2014; 15(1):1–9. https://doi.org/10.1186/1471-2369-15-95.
[2] Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 2013;8(9):1482–93. https://doi.org/10.2215/CJN.00710113.
[3] Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015;41(8):1411–23. https://doi.org/10.1007/s00134-015-3934-7.
[4] Chertow GM. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16(11):3365–70. https://doi.org/10.1681/ASN.2004090740.
[5] Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int 2012;81(5):477–85. https://doi.org/10.1038/ki.2011.405.
[6] Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81(5):442–8. https://doi.org/10.1038/ki.2011.379.
[7] Machado S, Figueiredo N, Borges A, Pais MSJ, Freitas L, Moura P, et al. Acute kidney injury in pregnancy: a clinical challenge. J Nephrol 2012;25(1):19–30. https://doi.org/10.5301/jn.5000013.
[8] Stratta P, Besso L, Canavese C, Grill A, Todros T, Benedetto C, et al. Is pregnancy-related acute renal failure a disappearing clinical entity? Ren Fail 1996;18(4):575–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8875682.
[9] Stratta P, Canavese C, Dogliani M, Todros T, Gagliardi L, Vercellone A. Pregnancy-related acute renal failure. Clin Nephrol 1989;32(1):14–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2788054.
[10] Prakash J, Niwas SS, Parekh A, Pandey LK, Sharatchandra L, Arora P, et al. Acute kidney injury in late pregnancy in developing countries. Ren Fail 2010;32(3):309–13. https://doi.org/10.3109/08860221003606265.
[11] Callaghan WM, Creanga AA, Kuklina EV. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. Obstet Gynecol 2012;120(5):1029–36. https://doi.org/10.1097/AOG.0b013e31826d60c5.
[12] Mehta RL, Cerdá J, Burdmann EA, Tonelli M, García-García G, Jha V, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet 2015; 385(9987):2616–43. https://doi.org/10.1016/S0140-6736(15)60126-X.
[13] Mehta RL, Burdmann EA, Cerdá J, Feehally J, Finkelstein F, García-García G, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. Lancet 2016;387(10032):2017–25. https://doi.org/10.1016/S0140-6736(16)30240-9.
[14] Cooke WR, Hemmilä UK, Craik AL, Mandula CJ, Mvula P, Msusa A, et al. Incidence, aetiology and outcomes of obstetric-related acute kidney injury in Malawi: a prospective observational study. BMC Nephrol 2018;19(1):25. https://doi.org/10.1186/s12882-018-0824-6.
[15] Fakhouri F, Vercel C, Frémeaux-Bacchi V. Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. Clin J Am Soc Nephrol: CJASN 2012;7(12):2100–6. https://doi.org/10.2215/CJN.13121211.
[16] Grünfeld JP, Pertuiset N. Acute renal failure in pregnancy: 1987. Am J Kidney Dis 1987;9(4):359–62. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0272638687801373.
[17] Gammill HS, Jeyabalan A. Acute renal failure in pregnancy. Crit Care Med 2005;33(10):S372–84. Available from: https://insights.ovid.com/crossref?an=00003246-200510001-00019.
[18] Liu S, Joseph KS, Bartholomew S, Fahey J, Lee L, Allen AC, et al. Temporal trends and regional variations in severe maternal morbidity in Canada, 2003 to 2007. J Obstet Gynaecol Can 2010;32(9):847–55. https://doi.org/10.1016/S1701-2163(16)34656-4.
[19] Joseph KS, Liu S, Rouleau J, Kirby RS, Kramer MS, Sauve R, et al. Severe maternal morbidity in Canada, 2003 to 2007: surveillance using routine hospitalization data and ICD-10CA codes. J Obstet Gynaecol Can 2010;32(9):837–46. https://doi.org/10.1016/S1701-2163(16)34655-2.
[20] Mehrabadi A, Liu S, Bartholomew S, Hutcheon JA, Magee LA, Kramer MS, et al. Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study. BMJ 2014 Jul 30;349:g4731. Available from: https://www.bmj.com/content/bmj/349/bmj.g4731.full.pdf.
[21] Kumar KS, Krishna CR, Kumar VS. Pregnancy related acute renal failure. J Obstet Gynaecol India 2006;56(4):308–10. Available from: http://medind.nic.in/jaq/t06/i4/jaqt06i4p308.pdf.
[22] Najar MS, Shah AR, Wani IA, Reshi AR, Banday KA, Bhat MA, et al. Pregnancy related acute kidney injury: a single center experience from the Kashmir Valley. Indian J Nephrol 2008;18(4):159–61. https://doi.org/10.4103/0971-4065.45291.
[23] Jeyabalan A, Conrad KP. Renal function during normal pregnancy and preeclampsia. Front Biosci 2007;12:2425–37. Available from:http://www.ncbi.nlm.nih.gov/pubmed/17127252.
[24] Lindheimer MD, Cunningham FG, Roberts JM, Chesley LC. Chesley's hypertensive disorders in pregnancy. 4th ed. 2014.
[25] Alper AB, Yi Y, Webber LS, Pridjian G, Mumuney AA, Saade G, et al. Estimation of glomerular filtration rate in preeclamptic patients. Am J Perinatol 2007;24(10):569–74. https://doi.org/10.1055/s-2007-986697.

[26] Smith MC, Moran P, Ward MK, Davison JM. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. BJOG An Int J Obstet Gynaecol 2008;115(1):109–12. https://doi.org/10.1111/j.1471-0528.2007.01529.x.
[27] Liu Y, Ma X, Zheng J, Liu X, Yan T. Pregnancy outcomes in patients with acute kidney injury during pregnancy: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2017;17(1):235. https://doi.org/10.1186/s12884-017-1402-9.
[28] KDIGO. Clinical practice guideline for acute kidney injury. Kidney Int Off J Int Soc Nephrol 2012;2(1):1–138. i-iv, Available from: http://www.kdigo.org/index.php.
[29] Fujii T, Uchino S, Takinami M, Bellomo R. Validation of the kidney disease improving global outcomes criteria for AKI and comparison of three criteria in hospitalized patients. Clin J Am Soc Nephrol 2014;9(5):848–54. https://doi.org/10.2215/CJN.09530913.
[30] Prakash J, Vohra R, Wani IA, Murthy AS, Srivastva PK, Tripathi K, et al. Decreasing incidence of renal cortical necrosis in patients with acute renal failure in developing countries: a single-centre experience of 22 years from Eastern India. Nephrol Dial Transplant 2007;22(4):1213–7. https://doi.org/10.1093/ndt/gfl761.
[31] Piccoli GB, Daidola G, Attini R, Parisi S, Fassio F, Naretto C, et al. Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. BJOG An Int J Obstet Gynaecol 2013;120(4):412–27. https://doi.org/10.1111/1471-0528.12111.
[32] Mehta RL, Mehta RL, Pascual MT, Pascual MT, Soroko S, Soroko S, et al. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. J Am Med Assoc 2002;288(20):2547–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16794108.
[33] Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Diuretics and mortality in acute renal failure. Crit Care Med 2004;32(8):1669–77.
[34] Chan WS, Walker MC, Rodger MA. De Swiet's medical disorders in obstetric practice. 5th ed. 2010. p. 730–5 Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84885726828&partnerID=tZOtx3y1.
[35] Kellum JA, Decker M. Use of dopamine in acute renal failure: a meta-analysis. Crit Care Med 2001;29(8):1526–31.
[36] Marik P. Low-dose dopamine: a systematic review. Intensive Care Med 2002;28(7):877–83. https://doi.org/10.1007/s00134-002-1346-y.
[37] Steyn DW, Steyn P. Low-dose dopamine for women with severe pre-eclampsia. Cochrane Database Syst Rev 2007;(1), CD003515. https://doi.org/10.1002/14651858.CD003515.pub2.
[38] Drakeley AJ, Le Roux PA, Anthony J, Penny J. Acute renal failure complicating severe preeclampsia requiring admission to an obstetric intensive care unit. Am J Obstet Gynecol 2002;186(2):253–6.
[39] Okundaye I, Abrinko P, Hou S. Registry of pregnancy in dialysis patients. Am J Kidney Dis 1998;31(5):766–73.
[40] NICE. Hypertension in pregnancy: diagnosis and management Guidance and guidelines NICE. NICE. 2015. Available from:, http://www.nice.org.uk/guidance/cg107.
[41] Lockwood CJ, Silver RM. Coagulation disorders in pregnancy. In: Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore, editors. Creasy & Resnik's maternal-fetal medicine: principles and practice. 6th ed., vol. 41. Philadelphia: Saunders Elsevier; 2009. p. 825–54.
[42] Huerta A, Arjona E, Portoles J, Lopez-Sanchez P, Rabasco C, Espinosa M, et al. A retrospective study of pregnancy-associated atypical haemolytic uremic syndrome. Kidney Int 2018;93(2):450–9. https://doi.org/10.1016/j.kint.2017.06.022.
[43] Kabbali N, Tachfouti N, Arrayhani M, Harandou M, Tagnaouti M, Bentata Y, et al. Outcome assessment of pregnancy-related acute kidney injury in Morocco: a national prospective study. Saudi J Kidney Dis Transpl 2015;26(3):619–24. https://doi.org/10.4103/1319-2442.157426.
[44] Hassan I, Junejo AM, Dawani ML. Etiology and outcome of acute renal failure in pregnancy. J Coll Phys Surg Pak 2009;19(11):714–7. https://doi.org/10.2009/JCPSP.714717.
[45] Alexopoulos E, Tambakoudis P, Bili H, Sakellariou G, Mantalenakis S, Papadimitriou M. Acute renal failure in pregnancy. Ren Fail 1993;15(5):609–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8290707.
[46] Dashe JS, Ramin SM, Cunningham FG. The long-term consequences of thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome) in pregnancy. Obstet Gynecol 1998;91(5 Pt I):662–8.
[47] Kaze FF, Njukeng FA, Kengne AP, Ashuntantang G, Mbu R, Halle MP, et al. Post-partum trend in blood pressure levels, renal function and proteinuria in women with severe preeclampsia and eclampsia in Sub-Saharan Africa: a 6-months cohort study. BMC Pregnancy Childbirth 2014;14:134. https://doi.org/10.1186/1471-2393-14-134.
[48] Unverdi S, Ceri M, Unverdi H, Yilmaz R, Akcay A, Duranay M. Postpartum persistent proteinuria after preeclampsia: a single-center experience. Wien Klin Wochenschr 2013;125(3–4):91–5. https://doi.org/10.1007/s00508-013-0320-8.