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Relation between acute kidney injury and pregnancy-related factors

Monchai Siribamrungwong*, Pawadee Chinudomwong

Department of Internal Medicine, Lerdsin General Hospital, College of Medicine, Rangsit University, Bangkok 10500, Thailand

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ABSTRACT

Acute kidney injury (AKI) is a serious problem during pregnancy. Once occurred, it brings about devastating maternal and fetal outcomes. Among developed nations, the trend of pregnancy-related AKI (PRAKI) is on a decline due to the advances in obstetrics care and the legality of abortion. On the contrary, this situation remains one of the major health problems in the developing countries. Though some improvements have been observed, PRAKI still causes high maternal morbidity and mortality, leading to fetal losses. This article aims to review current studies with regards to obstetrics related AKI. Most of the studies in this review were carried out in observational, both prospective and retrospective, studies. Results demonstrated a variety of major PRAKI causes such as hypertensive disorders in pregnancy, obstetric hemorrhage, sepsis, thrombotic microangiopathy and acute fatty liver in pregnancy. Aside from awareness of the etiologies of PRAKI, understanding the physiological renal adaptation during pregnancy is crucial for early detection, diagnosis, and proper management to prevent the obstetric complications.

1. Introduction

Acute kidney injury (AKI) was defined as an increase in serum creatinine within 2–7 days or oliguria. It affects 10%–20% of hospitalized adults and is associated with an increased risk of chronic kidney disease and further complications. The development of AKI in pregnancy, termed pregnancy-related AKI (PRAKI) is not rare, occurring between 6% and 55% cases. This condition contributes as one of the most common causes of AKI, contributing 20%–40% of all AKI cases[1]. The mortality rate remains very high and the risks for both maternal and fetal complications are also significant. PRAKI may be due to a decrease in renal perfusion or ischemic acute tubular necrosis (ATN) from a variety of conditions. These include hyperemesis gravidarum, postpartum hemorrhage, and renal cortical necrosis (RCN). Other specific pregnancy-related conditions such as preeclampsia, thrombotic microangiopathies (TMA), and acute fatty liver of pregnancy are also the significant etiologies of PRAKI.

*Corresponding author: Monchai Siribamrungwong, MD., Department of Internal Medicine, Lerdsin General Hospital, College of Medicine, Rangsit University, Bangkok 10500, Thailand.
Tel: +66 (0) 2 353 9800
Fax: +66 (0) 2 353 9756
E-mail: monsiri_dr@hotmail.com
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2. Renal physiological changes during pregnancy

Normal pregnancy accompanies a number of physical and psychological changes. The urinary tract is a system that demonstrates remarkable alterations in both anatomy and physiology. Understanding of these changes is crucial in evaluating renal diseases in pregnant women.

2.1. Anatomical changes

Initially, the size of the kidney increases by 1.0–1.5 cm in length[2–4]. Primarily, the change is in the collecting system[4]. This is the result of tissue hypertrophy[2], renal vascular and interstitial space expansion[3]. The renal pelvis, calyces and ureters are also dilated, expanding to the pelvic brim[4]. It is postulated that nearly 90% of normal pregnant women develop physiological hydronephrosis[2,3], with more pronounced dilatation noted on the right kidney[2,4]. This is probably due to the dextrorotation of the uterus and dilatation of right ovarian venous plexus[4], as evident from ultrasonography[2]. In addition, the gravid uterus causes partial extrinsic mechanical obstruction of the urinary tract[2,3]. The progesterone hormone directly exerts its effect of smooth muscle relaxation[2,5], while prostaglandin E2 inhibits ureteric tone and peristalsis[3]. All of these changes lead to urinary stasis, increased risk of bacterial overgrowth, and urinary tract infections[2,4]. These anatomic findings persist up to 12-week post-partum before returning to the pre-pregnancy state[4,5].

2.2. Physiological changes

In terms of kidney hemodynamics, renal plasma flow elevates by 5%–70%[4], and can reach up to 85% in the second trimester[3]. After conception, the glomerular filtration rate (GFR) increases continuously and the increment can be up to 25% at the 4th week of gestation[2]. It reaches a peak at 65% increase from the baseline at around the 13th week of gestation[3,4]. This consequently leads to hyperfiltration state, bringing other physiological changes such as an increase in uric acid clearance, increased excretion of calcium, glycosuria, increased filtration of amino acids, and increased creatinine clearance (Table 1). In addition to a lowered blood urea nitrogen (BUN) level[6], serum creatinine considerably falls to a pregnancy range of 0.4–0.8 mg/dL[2]. Hence, a serum creatinine level of $\geq$ 1.0 mg/dL, though within a normal limit in general population, signifies renal impairment in the pregnant population and prompts further investigations[3].

Table 1
Physiological changes of renal hemodynamics during pregnancy.

Increased	Decreased
Uric acid clearance	BUN
Excretion of glucose and calcium	Serum creatinine
Filtration of amino acids	Serum sodium, magnesium, and bicarbonate

2.3. Systemic hemodynamics

As early as the first trimester, systemic vascular resistance decreases as a result of peripheral vasodilation. The process is due to the synthesis of nitric oxide and relaxin[2–5]. In addition, vascular responsiveness is reduced as an effect of norepinephrine and angiotensin II[3,5]. Endothelial prostacyclin production, prolactin and progesterone levels are all increased[3].

Compensatory events include elevation of cardiac output by 40%–50%, the increase of resting heart rate[2,5], and the reduction of blood pressure in the first semester[2–4]. The drop in blood pressure reaches a nadir of approximately 10 mmHg of the systolic measurement in the mid-trimester before rising towards the pre-pregnancy level at term[2]. Plasma expansion results in an increase in blood volume by 50%[2–5], leading to subsequent anemia due to hemodilution. Additionally, normal pregnancy brings about osmotic reset due to decreased vasopressin secretion and thirst stimulation[3]. As a result, plasma osmolality and sodium concentration decrease. Furthermore, an increased progesterone level leads to hyperventilation, causing mild respiratory alkalosis, and decreasing serum bicarbonate level with a drop of about 4 mEq/L[3–5].

2.4. Incidence of PRAKI

The incidence of PRAKI is a more common problem in the developing nations[7,8]. In the developed nations, the lesser incidence of this problem is due to the improvement in antenatal care[1,7,9–11], and the reduction of septic abortion due to its legalization[3,9]. Socioeconomic factors contributing to PRAKI in the underdeveloped countries are mainly due to poverty, poor obstetrics care, lack of proper healthcare facilities and awareness of the condition, delayed referral process, multiparity, and the increasing population number[2,7,8].

All over the world, a decline in the incidence of PRAKI was observed over the past 50 years[9,11,12]. The incidence reduced from 20% to 40% in the 1960s to less than 10% in the recent years[9,13]. An increased drop in the incidence was seen in the western countries such as countries in Europe and North America. Some studies summarized that the incidence of PRAKI was 1.0%–2.8% in developed nations versus 4%–26% in developing nations[9,14,15].

In the developed nations, a study done in France demonstrated a decrease in rate of PRAKI from 40.0% to 4.5% over a 12-year period following the legalization of abortion[1]. Nevertheless, not all studies reported similar results. A recent retrospective cohort study carried out in Canada illustrated that the incidence of obstetric AKI was elevated in both Canada and the United States. The rate of PRAKI in Canada increased from 1.6 per 10000 deliveries in 2003 to 2.3 per 10000 deliveries in 2007. Data from the United States also showed that the rate increased from 2.3 to 4.5 per 10000 deliveries over a 10-year period between 1998 and 2008[12]. The reason for the growing rate of PRAKI, that is possibly not actual incidence, might be due to the increasing sensitivity of AKI diagnosis with close obstetric observation, particularly in high risk pregnancy. Moreover, the incidence of dialysis required PRAKI also declined[16].

In developing countries, a large number of studies on PRAKI were continually carried out, mostly seen from the African and the South Asian regions. There was some degree of improvement in the incidence of PRAKI. A study from India revealed a decrease in PRAKI incidence from 22% between 1965 and 1974 to 9% between 1981 and 1986. This was due to the availability of medical facilities and better obstetric care. Similarly, PRAKI in South Africa showed improvement from 25% to less than 16% over a period of 15 years[8]. A study in Turkey also demonstrated a declination of PRAKI in relation to the reduction in septic abortion by 30% in the last 20 years. This was due to the improved socioeconomic situation, early detection of PRAKI, and proper management of obstetric complications[17,18].

2.5. Definition and diagnosis of PRAKI

For the general population, the risk, injury, failure, loss of kidney function, and end-stage renal failure criterion was the first classification system for AKI created by the Acute Dialysis Quality Initiative in 2002. Currently, the Kidney Disease Improving Global Outcomes created the clinical practice guidelines for AKI. AKI was defined by an increase in serum creatinine (1.5 times the normal baseline within 7 days) or urine output of less than 0.5 mL/kg per hour for 6 h. Subsequently, the definition was extended to include an increase in serum creatinine $\geq$ 0.3 mg/dL within 2 days (Table 2)[19].

Unfortunately, the mentioned definition of AKI is not valid for pregnant women due to the physiological changes during pregnancy. The renal function evaluation by eGFR is also inaccurate. This poses potential challenges for involving clinicians because the diagnostic definition is not universally conceptualized[3]. From the previously published studies, PRAKI was diagnosed by an acute increase in serum creatinine of 0.1–0.5 mg/dL from baseline, a failure of serum creatinine to decrease from baseline, or serum creatinine more than 1–2 mg/dL[1–4,6–12,14–18,20–23].

Table 2
AKI classifications.

Guideline		Serum creatinine criteria	Minimum time period of AKI occurring
RIFLE	Risk	Increase in serum creatinine $\geq$ 1.5 times baseline Decrease in eGFR $\leq$ 25%	Serum creatinine changes over 1–7 days, sustained for more than 24 h
	Injury	Increase in serum creatinine $\geq$ 2.0 times baseline Decrease in eGFR $\geq$ 50%	
	Failure	Increase in serum creatinine $\geq$ 3.0 times baseline Decrease in eGFR $\geq$ 75% Absolute serum creatinine $\geq$ 4 mg/dL with an acute rise of at least 0.5 mg/dL	
KDIGO	Stage 1	Increase in serum creatinine $\leq$ 1.5 times baseline Increase serum creatinine $\geq$ 0.3 mg/dL	Definition of AKI requires serum creatinine changes $\geq$ 1.5 times baseline to have occurred within 7 days Serum creatinine increases 0.3 mg/dL within 48 h
	Stage 2	Increase in serum creatinine > 2 times baseline	
	Stage 3	Increase in serum creatinine $\geq$ 3 times baseline Absolute serum creatinine $\geq$ 4 mg/dL	

RIFLE: Risk, injury, failure, loss of kidney function, and end-stage renal failure; eGFR: Estimated GFR; KDIGO: Kidney Disease Improving Global Outcomes.

Studies were performed to evaluate and compare the accuracy of two widely used eGFR formulas, the modification of diet in renal disease and the Cockcroft-Gault equations. The results concluded that both formulas were inaccurate in assessing the GFR in this particular population. While the Cockcroft-Gault equation overestimated the GFR, the modification of diet in renal disease formula underestimated the real GFR value by about 40 mL/min[3,4]. But the latter might be slightly better in estimating GFR among the preeclampsia patients[4]. As such, the gold standard method for GFR estimation in pregnant women was creatinine clearance by a 24-h urine collection[3,4]. Guo *et al.* demonstrated a negative correlation between serum cystatin C and 24-h urine creatinine clearance when compared with serum creatinine and uric acid in normal pregnancies and severe preeclampsia[24]. On the contrary, Saxena *et al.* reported that the serum cystatin C did not correlate with inulin clearance in pregnancy and postpartum women[25]. Therefore, the use of cystatin C for measurement of GFR in pregnancy cannot be recommended at this time[25].

Currently, there are many biomarker studies for AKI prediction, but studies in the pregnant population group are limited. Patel *et al.* reported that serum neutrophil gelatinase-associated lipocalin (NGAL) level was significantly associated with serum creatinine in the Indian pregnant population with hypertension[26]. Serum NGAL level in oliguric patients was significantly higher compared with nonoliguric patients. Serum NGAL level also had a positive correlation with disease severity including blood pressure level, BUN, serum creatinine, and serum uric acid in hypertensive pregnant patients[27]. Xiao *et al.* evaluated a combination of biomarkers for diagnosing AKI with considerable accuracy in preeclampsia[28]. Serum cystatin C, urine retinol-binding protein, urine NGAL and urine kidney injury molecule-1 levels in the preeclampsia group were higher than the normal pregnancy group. When these markers were combined, the sensitivity and specificity for diagnosing AKI were almost 100%[28].

3. Etiologies of PRAKI

Current studies have shown a variety of major etiologies of PRAKI. The main causes mentioned in the literature are hypertensive disorders in pregnancy[12–14,21,22], TMA[17], sepsis[29], obstetrics hemorrhages[8,11,18,30], and septic shock[7]. A number of researches pointed out that PRAKI occurred in a bimodal distribution[1,9,15,31,32]. The first observed peak is between the 7th and 16th week of gestation, and the second peak is noted between the 34th and 36th week of gestation[9,15,31].

4. Early trimester

The two main etiologies of obstetric AKI during this trimester include pre-renal azotemia resulting from hyperemesis gravidarum, and sepsis due to septic abortion. In hyperemesis gravidarum, severe vomiting and poor maternal intake will trigger volume depletion, leading to AKI. Hyperemesis gravidarum can be diagnosed by the history of persistent vomiting and is typically associated with metabolic alkalosis[5]. The symptoms often aggravated by strong odors, hot food, and delayed gastric emptying[4]. Hospitalization and supportive treatment with intravenous fluid replacement and anti-emetic treatment are warranted in the cases of severe dehydration.

Some studies reported septic abortion as the most common cause of PRAKI[7,9,20,29]. AKI is associated with this condition for many reasons. Volume depletion and hypotension from hemorrhage or sepsis may lead to considerable renal ischemia. In addition, soap, some disinfectants, and common abortifacients may have specific nephrotoxic effects. A study done by Najar *et al.* illustrated that septic abortion accounted for 50% of PRAKI cases, with 75% occurring in the first trimester and 25% in the second trimester[9]. A study carried out in Bangladesh also showed similar results, demonstrating that septicemia or post-abortion sepsis was the main reason of PRAKI. In addition to irregular or absent antenatal care, low education[7], and home births[29], most of the PRAKI patients were from rural areas where abortions were performed by untrained midwives[9], local village practitioners or traditional birth attendants[20].

Furthermore, this condition is usually lethal if the causative organism is *Clostridium* spp. The patient often manifests symptoms of abdominal pain, vomiting, and jaundice, within hours to a few days. Laboratory findings may illustrate anemia, leukocytosis, thrombocytopenia, oliguria, and electrolyte imbalances[4,9]. ATN is the most common finding of PRAKI and has a good prognosis as compared to other pathological findings[33]. Administrations of proper antibiotics, volume resuscitation, appropriate supportive treatment, and dialysis when indicated, are the mainstay of management to bring a complete recovery without complications[4,34].

5. Late trimester

5.1. Hypertensive disorders of pregnancy

Numerous studies reported this condition as the most common cause of PRAKI[4,12–14,22]. The maternal mortality rate was reported between 6% and 30%[14]. Predilection of hypertensive disorders of pregnancy peaks at two settings: young primigravida and older multiparous women. Spectrum of hypertension disorders of pregnancy can be classified into five categories: chronic hypertension, preeclampsia, eclampsia, gestational hypertension and preeclampsia superimposed on chronic hypertension. Among these entities, studies revealed that preeclampsia and eclampsia accounted for most of PRAKI cases. Hypertensive disorders in pregnancy occur in about 7% of all pregnancies and it remains the leading cause of maternal-fetal mortality. It is also associated with intrauterine growth restriction and small for gestational age babies[4].

Preeclampsia is defined as the new onset of persistent hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg) accompanied with proteinuria > 300 mg per day, after the 20th week of gestation[4,5,11]. Eclampsia is defined as preeclampsia with the presence of seizure[5]. Etiologies of preeclampsia are said to be multi-factorial. Maternal risk factors can be grouped into three major factors: obstetric factors, co-morbid factors and genetic factors (Table 3).

The pathogenesis of preeclampsia is due to utero-placental ischemia from a combination of genetic and environmental factors, leading to inadequate invasion of uterine spiral arteries by the placental trophoblast. This in turn affects the ability of uterine vessels to transform from the high to the low resistance channels. The ensuing placental ischemia may stimulate production of a soluble fms-like tyrosine kinase-1 (sFlt-1). The protein is a circulating anti-angiogenic factor that antagonizes the angiogenic and vasodilatory effects of vascular endothelial and placental growth factors[35]. Other factors leading to preeclampsia include an imbalance of vasoactive substances, endothelial dysfunction, and absence of physiologic renal alteration seen in normal pregnancy[4].

The severity of preeclampsia is classified as mild and severe, characterized by the blood pressure level, proteinuria, and associated end organ damages (Table 4).

The most common presenting symptoms in preeclampsia are epigastric or right upper quadrant pain, followed by renal involvement, which manifests as a dropped GFR and renal plasma flow[3]. Laboratory investigations include hematocrit level, platelet count, serum creatinine, liver aminotransferases, serum lactate dehydrogenase (LDH), uric acid concentration, and coagulation profile. In addition, fetal monitoring tests such as non-stress test and biophysical profile should also be done[4].

Management of preeclampsia consists of maternal blood pressure control with both pharmacological and non-pharmacological treatment. Frequent assessment of the fetal well-being is performed by daily fetal movement count or non-stress test and Doppler velocimetry. Delivery is the ultimate treatment for this condition. The decision on the timing of delivery is based on the gestational age, maternal and fetal condition, as well as the severity of the disease itself[4]. Prompt delivery is indicated when there is worsening maternal condition, and signs of severe fetal distress[3].

Hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome is a variant form of severe preeclampsia[3,4,11]. There is a significant liver involvement, but nearly 20% of affected patients have neither hypertension nor proteinuria[4]. Abnormal laboratory findings include hemolysis presenting with anemia, decreased haptoglobin, raised LDH, elevated liver function tests, and low platelet count[3,11]. Thrombocytopenia is the first abnormality to be detected and a marker of disease severity. Approximately 70% of cases develop the disease before delivery and it has a peak incidence between the 27th and 37th week of gestation. In addition to elevated sFlt-1 level, soluble endoglin which is a placental-derived soluble transforming growth factor-beta co-receptor, is also elevated. It acts synergistically with sFlt-1 and potentiates more maternal endothelial dysfunction[36]. The principal management of HELLP syndrome is supportive care with timely delivery based on gestational age and overall materno-fetal condition[11].

5.2. TMA

TMA are rare in the pregnant population. It affects about 1 per 25 000 gestations. TMA in pregnancy accounts for 8%–18% of all TMA cases[37,38]. The disease is defined by the presence of fibrin and/or platelet thrombi in the microcirculation of multiple organs, predominantly the kidney and the brain. Other pathologic features include endothelial cell swelling, accumulation of protein and cell debris in the subendothelial layer of blood vessels, and splitting of the glomerular basement membrane[3,36]. This syndrome comprises thrombotic thrombocytopenic purpura (TTP), affecting mainly the brain; and hemolytic uremic syndrome (HUS), affecting mainly the kidney. Nevertheless, differentiation between the two entities may be difficult since 10% of TTP patients have significant AKI and neurological involvement is not uncommon in HUS[3,5,39].

TTP is characterized by thrombocytopenia, hemolysis and a variety of organ dysfunctions, particularly involving the renal and neurological systems. TTP in pregnancy usually takes place in the late trimester or during the postpartum period. The significant pathogenic feature is the gradual fall of von Willebrand factor cleaving protease or a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 as gestational age progresses. This alters the hemostatic status during pregnancy. This condition is difficult to differentiate from severe preeclampsia with HELLP syndrome due to their overlapping characteristics. The usual clinical presentation of TTP consists of bruises, fatigue, abdominal pain, nausea, vomit, and a variety of neurologic symptoms ranging from lethargy to seizure. Renal involvement is found to be as high as 30%–80% in pregnancy-related TTP, mainly presenting with proteinuria and hematuria. The mainstay of treatment involves plasma exchanges or fresh frozen plasma infusions, aimed to restore a significant enzymatic activity. This by far decreases the maternal mortality remarkably[11]. Systemic steroid is used as an adjunctive therapy, but no definite evidence has proven its efficacy.

Pregnancy-related HUS is mainly associated with alternative C3 convertase dysregulation[37]. It is a syndrome consisting of microangiopathic hemolyticanemia, thrombocytopenia, and renal failure. This condition somewhat overlaps with severe preeclampsia accompanied by HELLP syndrome. However, there are some distinguishing features between HUS and HELLP syndromes. HUS is associated with the complement

Table 3
Maternal risk factors of preeclampsia.

Obstetric factors	Co-morbid factors	Genetic factors
Nulliparous/primigravida	Chronic hypertension	Anti-phospholipid antibody
Age > 35 or < 16 years	Renal disease	Factor V Leiden mutation
Multiple gestation pregnancy	Rheumatic disease	Preeclampsia in first-degree relative pregnancy
History of preeclampsia	Pre-existing diabetes mellitus	
Molar pregnancy	Obesity	

Table 4
Classification of preeclampsia and its characteristic features.

Characteristics	Mild	Severe
Blood pressure	Systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg, on 2 occasions 6 h apart (in previously normotensive individuals before 20 weeks of gestation)	Systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 110 mmHg, on 2 occasions 6 h apart
Proteinuria (24-h collection)	≥ 300 mg	≥ 5 g
Associated symptoms	No evidence of end-organ damage	Epigastric or right upper quadrant pain and/or impaired liver function Visual disturbances Persistent headache Altered sensorium Ankle edema Pulmonary edema Thrombocytopenia (platelet < 100000) Oliguria (urine output < 400 mL/day)

alternative pathway dysregulation which usually occurs during the postpartum period and there is an isolated increase of LDH. Elevated transaminases are found in preeclampsia and HELLP syndrome. Additionally, prolonged prothrombin time and partial thromboplastin time are more suggestive of preeclampsia. The treatment of HUS is plasma exchange, aiming to remove the dysfunctional complement cascade components and supply normal complement regulatory factors[1].

5.3. Acute fatty liver of pregnancy (AFLP)

AFLP is an infrequent complication and typically occurs after the 34th week of gestation[5], it is counted as an obstetrics emergency condition[1,3]. The condition is more commonly observed in the nullipara and primigravida[4]. The incidence is between 1 per 7000 gestations to 1 per 20000 gestations. Several studies reported that maternal and perinatal mortality rate is between 10% and 20%[3]. Being autosomal recessive, an erroneous gene causes excessive fetal fatty acid accumulation and its release into the maternal circulation. Such fatty acid deposits in the maternal hepatic tissue and impairs the liver function[3,4]. The histological finding illustrates microvascular fatty infiltration of hepatocytes without inflammation or necrosis[3,5].

The diagnosis is based on clinical and laboratory findings. During the late trimester, pregnant women may manifest with abdominal pain, nausea, vomit, malaise, anorexia, and jaundice[3,5,11]. The severity of liver impairment varies, ranging from moderate isolated transaminase elevations to fulminant hepatic failure with encephalopathy. In addition, kidney involvement that clinically resembles hepato renal syndrome can be presented in around 60% of patients[1]. Acute kidney dysfunction is typically nonoliguric, whereby proteinuria and peripheral edema are common. Fortunately, renal recovery usually follows delivery and dialysis is rarely required. Laboratory abnormalities include hyperbilirubinemia, normal or elevated aminotransferase, coagulopathy, anemia and hypoglycemia[3,5,11]. AFLP is a diagnosis of exclusion, having to rule out viral hepatitis and biliary obstruction[11]. The definite diagnosis is confirmed with a liver biopsy[3,4].

Management is generally a supportive care and immediate delivery with caesarean section being the preferred choice of delivery[4]. Anemia and coagulopathy are corrected by transfusion of blood products. Hepatic encephalopathy can be managed with high carbohydrate, low-protein diet, and oral lactulose[11]. Most patients will recover completely after delivery and liver transplantation is rarely necessary.

5.4. Puerperal sepsis

Several studies demonstrated that puerperal sepsis was the leading cause of PRAKI[15,29,31,32,40]. The rate of maternal mortality varied between 18% and 30%[40]. As defined by the World Health Organization, puerperal sepsis is a genital tract infection occurring at any time between the rupture of amniotic membrane and labor or 42 days postpartum. Two or more of these conditions have to be presented: fever (≥ 38.5 °C), pelvic pain, abnormal odor or foul-smelling vaginal discharges, and delayed uterine involution. Major causes are prolonged rupture of membrane, obstructed labor, and frequent vaginal examination. Sources of infection are retained product of conception, urinary tract infection and mastitis. Causative organisms include Gram-positive *Streptococcus pyogenes*, *Staphylococcus aureus*, coliform bacteria, *Chlamydia* spp. and *Clostridium tetani*[3].

Fever and edema are also the major presentations that consist of up to 82.4% of cases. Other clinical manifestations comprise of dyspnea, vaginal bleeding, oliguria or anuria, changes in

sensorium, and convulsion[40]. Significant laboratory findings are anemia, leukocytosis, thrombocytopenia, hypo/hypernatremia, hypo/hyperkalemia, metabolic acidosis, proteinuria, hyperbilirubinemia, and positive fibrin degradation products[15,31,32]. Management generally includes the use of appropriate antibiotics and removal of the underlying infection[3].

5.5. Obstetrics hemorrhage

Few studies mentioned hemorrhage as a major cause of PRAKI with postpartum hemorrhage on the lead[18,30]. Blood loss leads to symptoms such as anuria and oliguria. The most common clinical diagnosis was ischemic ATN[23], as a result of hypoperfusion. The main causes of this condition are similar to those of septicemia, including home births, delivery by traditional birth attendants, and lack of proper facilities for blood loss management. Intravenous volume repletion and blood transfusion are needed to stabilize and correct the circulatory perfusion.

5.6. RCN

RCN is a rare condition resulting from severe reduction of renal perfusion caused by vascular spasm, microvascular injury, or intravascular coagulation. Pregnancy complications are the major risk factors of pregnancy-related RCN, which accounted for nearly 50% of total RCN cases. They include placental abruption, placenta previa, septic abortion, prolonged intrauterine fetal death, and amniotic fluid embolism. Patients may present with the abrupt onset of oliguria, gross hematuria, flank pain, hypotension, vaginal bleeding, contraction of the uterus, and symptoms of eclampsia. With imaging studies, ultrasonography initially shows enlargement of the kidneys with reduced blood flow. CT scan is the most sensitive imaging modality. It may reveal an absent opacification of the renal cortex, and enhancement of subcapsular and juxtamedullary areas and of the medulla without excretion of contrast medium. The important prognostic factors are the extent of necrosis, duration of oliguria, and severity of associated conditions. The cornerstone of management is to restore hemodynamic stability, usage of dialysis as indicated, and treatment of the underlying diseases. Unfortunately, not all patients have full renal function recovery, depending on the extent of necrosis[41].

6. Management

Management of PRAKI requires a lot of resources and involves a multidisciplinary team of medical specialists, as well as early detection and prompt intervention. Provision of care should be executed early, timely, and correctly. Model of PRAKI care should be targeted to the following aspects: hemodynamic stabilization, maternal and fetal monitoring, and treatment of underlying conditions[3,11].

Hemodynamic status can be optimized by adequate fluid replacement to correct volume deficit, electrolyte correction, control of bleeding, and blood transfusion when necessary[2]. Blood pressure should also be controlled in hypertensive pregnant women[3]. These could minimize the progression of further kidney damage. In certain situations, renal replacement therapy of any modalities may be initiated. Medical indication for dialysis remains the same as in the non-pregnant populations[2,3,6].

Monitoring of maternal blood pressure, renal function tests, and urine protein examination[5], are necessary and should be performed frequently in order to early detect any abnormalities. Fetal monitoring can be done by several methods. Evaluation of the fetus at the gestational age of less than 25 weeks is limited to Doppler auscultation. Other more sensitive methods that can be deployed at the later age of gestation comprise of fetal movement assessment, contraction stress test, and biophysical profile[6]. Regular fetal monitoring is helpful in early detection of fetal distress.

Importantly, the underlying diseases should always be identified and treated. For instance, the proper use of antibiotics according to the culture and sensitivity is essential in cases of infection. Fluid and electrolytes repletion is warranted in those presented with hyperemesis gravidarum. Blood transfusion should be rendered to those with massive obstetric hemorrhage. Management of preeclampsia is targeted to blood pressure control, prevention of seizure, and timely delivery[2]. In TMA, treatment with plasmapheresis is proper and efficient to increase maternal survival[1,3]. In AFLP, correction of coagulopathy with blood components, hypoglycemic prevention with adequate glucose administration, and hepatic encephalopathy treatment with low-protein diet and oral lactulose are all essential to stabilize the mother[3].

7. Conclusions

Due to an array of systemic and physiologic renal changes, PRAKI is a serious condition. Once occurred, it results in devastating materno-fetal outcomes and hence, remains a critical obstetrics complication. Apparently, its incidence is on a decline among developed nations owing to the improvement of obstetrics care and the legality of pregnancy termination. Studies had been performed to evaluate the causes of PRAKI and findings had been extensively varied. In relation to certain gestational periods, particular etiologies were identified accordingly. The most common causes of PRAKI in the early trimester include pre-renal azotemia from hyperemesis gravidarum and septic abortion. During the late trimester, major causes of PRAKI involve hypertensive disorders in pregnancy, TMA, AFLP and postpartum hemorrhage. Finally, the most effective method in dealing with this life-threatening situation is prevention. This is done through provision and promotion of maternal education, high-quality and accessible antenatal care with extensive obstetrics facilities, early detection and diagnosis of the condition, and timely management of obstetrics complications.

Conflict of interest statement

The authors report no conflict of interest.

References

[1] Hou S, Peano C. Acute renal failure in pregnancy. *Saudi J Kidney Dis Transpl* 1998; **9**(3): 261-6.
[2] Khanal N, Ahmed E, Akhtar F. Epidemiology, causes and outcome of obstetric acute kidney injury. In: Vijayakumar S, editor. *Novel insights on chronic kidney disease, acute kidney injury and polycystic kidney disease*. Rijeka: InTech; 2012, p. 67-81.
[3] Machado S, Figueiredo N, Borges A, São José Pais M, Freitas L, Moura P, et al. Acute kidney injury in pregnancy: a clinical challenge. *J Nephrol* 2012; **25**(1): 19-30.

[4] Sahay M. Acute kidney injury in pregnancy. In: Sahay M, editor. *Basic nephrology and acute kidney injury*. Rijeka: InTech; 2012, p. 151-72.
[5] Krane NK. Renal disease and pregnancy. New York: Medscape; 2013. [Online] Available from: http://emedicine.medscape.com/article/246123-overview [Accessed on 17th March, 2015]
[6] Alsuwaida A. Challenges in diagnosis and treatment of acute kidney injury during pregnancy. *Nephrourol Mon* 2012; **4**(1): 340-4.
[7] Rahman S, Gupta RD, Islam N, Das A, Shaha AK, Khan MAI, et al. Pregnancy related acute renal failure in a tertiary care hospital in Bangladesh. *J Med* 2012; **13**: 129-32.
[8] Ansari MR, Laghari MS, Solangi KB. Acute renal failure in pregnancy: one year observational study at Liaquat University Hospital, Hyderabad. *J Pak Med Assoc* 2008; **58**(2): 61-4.
[9] 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**: 159-61.
[10] Prakash J. The kidney in pregnancy: a journey of three decades. *Indian J Nephrol* 2012; **22**: 159-67.
[11] Ganesan C, Maynard SE. Acute kidney injury in pregnancy: the thrombotic microangiopathies. *J Nephol* 2011; **24**(5): 554-63.
[12] Mehrabadi A, Liu SL, 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; **349**: g4731.
[13] 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; http://dx.doi.org/10.5402/2013/109034.
[14] Bentata Y, Housni B, Mimouni A, Azzouzi A, Abouqal R. Acute kidney injury related to pregnancy in developing countries: etiology and risk factors in an intensive care unit. *J Nephrol* 2012; **25**(5): 764-75.
[15] Aggarwal RS, Mishra VV, Jasani AF, Gumber M. Acute renal failure in pregnancy: our experience. *Saudi J Kidney Dis Transpl* 2014; **25**(2): 450-5.
[16] Lunn MR, Obedin-Maliver J, Hsu CY. Increasing incidence of acute kidney injury: also a problem in pregnancy? *Am J Kidney Dis* 2015; **65**(5): 650-4.
[17] Altintepe L, Gezginç K, Tonbul HZ, Çelik Ç, Güney İ, Gezginç ST, et al. Etiology and prognosis in 36 acute renal failure cases related to pregnancy in central anatolia. *Eur J Gen Med* 2005; **2**(3): 110-3.
[18] Rizwan N, Uddin SF. Obstetrical acute renal failure: a challenging medical complication. *J Ayub Med Coll Abbottabad* 2011; **23**(4): 66-8.
[19] Mehat RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**(2): R31.
[20] Krishna A, Singh R, Prasad N, Gupta A, Bhadauria D, Kaul A, et al. Maternal, fetal and renal outcomes of pregnancy-associated acute kidney injury requiring dialysis. *Indian J Nephrol* 2015; **25**(2): 77-81.
[21] Fakhouri F, Vercel C, Frémeaux-Bacchi V. Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. *Clin J Am Soc Nephrol* 2012; **7**: 2100-6.
[22] Jeon DS, Kim TH, Lee HH, Byun DW. Acute renal failure during pregnancy. *Open J Nephrol* 2013; **3**: 11-2.
[23] Acharya A, Santos J, Linde B, Anis K. Acute kidney injury in pregnancy-current status. *Adv Chronic Kidney Dis* 2013; **20**(3): 215-22.
[24] Guo HX, Wang CH, Li ZQ, Gong SP, Zhou ZQ, Leng LZ, et al. The application of serum cystatin C in estimating the renal function in women with preeclampsia. *Reprod Sci* 2012; **19**(7): 712-7.
[25] Saxena AR, Ananth Karumanchi S, Fan SL, Horowitz GL, Hollenberg NK, Graves SW, et al. Correlation of cystatin-C with glomerular filtration rate by inulin clearance in pregnancy. *Hypertens Pregnancy* 2012; **31**(1): 22-30.
[26] Patel ML, Sachan R, Gangwar R, Sachan P, Natu SM. Correlation of serum neutrophil gelatinase-associated lipocalin with acute kidney injury in hypertensive disorders of pregnancy. *Int J Nephrol Renovasc Dis* 2013; **6**: 181-6.
[27] Sachan R, Patel M, Gaurav A, Gangwar R, Sachan P. Correlation of serum neutrophil gelatinase associated lipocalin with disease severity in hypertensive disorders of pregnancy. *Adv Biomed Res* 2014; **3**: 223.
[28] Xiao J, Niu J, Ye X, Yu Q, Gu Y. Combined biomarkers evaluation for diagnosing kidney injury in preeclampsia. *Hypertens Pregnancy* 2013; **32**(4): 439-49.
[29] Patel ML, Sachan R, Radheshyam N, Sachan P. Acute renal failure in pregnancy: tertiary centre experience from north Indian population. *Niger Med J* 2013; **54**(3): 191-5.
[30] Hassan I, Junejo AM, Dawani ML. Etiology and outcome of acute renal failure in pregnancy. *J Coll Physicians Surg Pak* 2009; **19**: 714-7.
[31] Kumar KS, Krishna CR, Kumar VS. Pregnancy related acute renal failure. *J Obstet Gynecol India* 2006; **56**(4): 308-10.
[32] Sivakumar V, Sivaramakrishna G, Sainaresh VV, Sriramnaveen P, Kishore CK, Rani ChS, et al. Pregnancy-related acute renal failure: a ten-year experience. *Saudi J Kidney Dis Transpl* 2011; **22**(2): 352-3.
[33] Davision JM, Lindheimer MD. Renal disorders. In: Greasy RK, Resnik R, Iams JD, editors. *Maternal-fetal medicine: principles and practices*. 5th ed. Philadelphia: Elsevier; 2004, p. 901-23.
[34] Srinil S, Panaput T. Acute kidney injury complicating septic unsafe abortion: clinical course and treatment outcomes of 44 cases. *J Obstet Gynaecol Res* 2011; **37**(11): 1525-31.
[35] Makris A, Thornton C, Thompson J, Thomson S, Martin R, Ogle R, et al. Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. *Kidney Int* 2007; **71**: 977-84.
[36] Vesely SK, George JN, Lämmle B, Studt JD, Alberio L, El-Harake MA, 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.
[37] Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, Couzi L, et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol* 2010; **21**: 859-67.
[38] Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, 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.
[39] Koehl B, Boyer O, Biebuyck-Gougé N, Kossorotoff M, Frémeaux-Bacchi V, Boddaert N, et al. Neurological involvement in a child with atypical hemolytic uremic syndrome. *Pediatr Nephrol* 2010; **25**(12): 2539-42.
[40] Arora N, Mahajan K, Jana N, Taraphder A. Pregnancy-related acute renal failure in eastern India. *Int J Gynaecol Obstet* 2010; **111**: 213-6.
[41] Prakash J, Tripathi K, Pandey LK, Gadela SR, Raja U. Renal cortical necrosis in pregnancy-related acute renal failure. *J Indian Med Assoc* 1996; **94**(6): 227-9.