

Pregnancy-related acute kidney injury: An analysis of 165 cases

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ABSTRACT

Pregnancy-related acute kidney injury (PRAKI) contributes to 3–7% of overall acute kidney injury (AKI) cases in Indian subcontinent. The aim of this study was to determine the outcomes of PRAKI and risk factors associated with renal injury and maternal mortality. One hundred and sixty-five patients with PRAKI, seen at M. S. Ramaiah Medical College between 2005 and 2014, were included in this, observational study. AKI was analyzed in terms of maximal stage of renal injury attained as per Risk, Injury, Failure, Loss of function, and End-stage renal disease (RIFLE) criteria. Outcomes included requirement for renal replacement therapy (RRT), maternal, and fetal mortality. Incidence of PRAKI was 1.56%, and the mean age of the study population was 25 years. Fifty percent of the patients were diagnosed with PRAKI during their first pregnancy. PRAKI was observed most commonly in the postpartum period (60%), followed by third trimester (32%); as per RIFLE criteria, failure was seen in 36% and injury in 34%. Thirty percent of cases required RRT. Sepsis (59%), pre-eclampsia, and eclampsia (56%) were the leading causes of PRAKI, while sepsis was the leading cause of maternal mortality. Maternal and fetal mortality were 20% and 22%, respectively. In univariate analysis, shock, hemorrhage requiring transfusion of >5 units packed red blood cells, oliguria, and “Loss” category of RIFLE were significantly associated with mortality. Majority of the patients (57%) required Intensive Care Unit care with a mean duration of admission at 7.3 days, and 75% was diagnosed with AKI at the time of admission. We report the lowest incidence of PRAKI in contemporary Indian literature. PRAKI was associated with high maternal and fetal mortality, with sepsis being the leading cause. No association was noted between mortality and initial stages of RIFLE criteria.

Key words: Obstetric renal failure, pregnancy-related acute kidney injury, RIFLE

Introduction

Pregnancy-related acute kidney injury (PRAKI) is a major cause of maternal and fetal morbidity and mortality in developing countries. With improvement in antenatal and postnatal care, the incidence of PRAKI in India has steadily declined from 22% in 1960s to 9% in 1980s,^[1] and further down to 3–7% in 2000s;^[2,3] however, the levels continue to remain

higher than the levels seen in developed countries (1 in 20,000 pregnancies).^[4] In developing countries, sepsis and hemorrhage account for >50% of cases of PRAKI,^[5,6] in contrast to developed countries where chronic hypertension, renal disease and preeclampsia and eclampsia are important causes.^[7,8] Cortical necrosis (CN) is an important cause of death and dialysis dependency in this population.^[9]

The aim of our study was to study the clinical characteristics and outcomes of patients with PRAKI at our institution and review the recent literature on this topic.

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Materials and Methods

In this prospective, observational study, 165 pregnant patients with a diagnosis of acute kidney injury (AKI) were admitted to our institution from 2005 to 2014. Records were analyzed for demographic characteristics, obstetric history, and clinical profile on admission. We excluded patients with preexisting diabetes mellitus, hypertension, contracted kidney, renal transplant recipients, or chronic kidney disease (CKD). CKD was defined as serum creatinine (S.cr) >1.5 mg/dl or presence of proteinuria >1+ on dipstick. Renal biopsy was done in patients with no renal recovery in terms of reduction in S.cr, urine output (u/o), or requirement of dialysis after 6 weeks from the time of diagnosis.

Definitions

AKI was defined on the basis of Risk, Injury, Failure, Loss of function, and End-stage renal disease (RIFLE) criteria.^[10] PRAKI was defined as AKI diagnosed anytime during pregnancy or during postpartum phase (first 6 weeks postdelivery).

Pre-eclampsia was defined as blood pressure reading >140/90 mmHg diagnosed for the first time after 20 weeks of gestation with $\geq 2+$ proteinuria on the dipstick.

Eclampsia was defined as the presence of new-onset grand mal seizures in a woman with pre-eclampsia.^[11]

Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome was defined by the combination of thrombocytopenia (<100 G/L), elevated liver enzymes (aminotransferase >70 UI/L), and hemolysis.

Sepsis was defined as per the criteria laid down by the American College of Chest Physicians.^[12] Sepsis is the clinical syndrome that results from a dysregulated inflammatory response to an infection that is nonresolving and deleterious, often leading to organ dysfunction. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection.

Outcomes

Evaluated outcomes included mortality, recovery of renal function or requirement of renal replacement therapy (RRT) and proteinuria. Renal recovery was defined as a decline in S.cr to ≤ 1.0 mg/dl and the presence of 24 h urine protein (UP) of <150 mg/day within 6 weeks of diagnosis of AKI. Patients who did not satisfy the criteria for renal recovery were subjected to a renal biopsy.

Statistical analysis

Data were analyzed using SPSS software version 18.0 by IBM. Chi-square test was used to find the factors associated with the outcome. Statistical significance was tested at $P < 0.05$. Risk estimate was calculated, and its 95% confidence interval was analyzed. Results are given as number, mean, median, and interquartile range for quantitative variables, and percentages for nominal variables.

Results

One hundred and sixty-five patients satisfied the criteria for PRAKI with an incidence of 1.56% in the context of all cases of AKI during the time period. Of these, five patients were lost to follow-up and have been excluded from the analysis related to renal and patient outcomes. The mean age of patients was 25 years. The majority of the patients were aged between 21 and 25 years (66%). Fifty percent of the patients were diagnosed with PRAKI during their first pregnancy. PRAKI was observed most commonly in the postpartum period (60%), followed by third trimester (32%). Ninety-three percent of women reported receiving antenatal care whereas 94% of patients delivered or aborted in an institutional setting. Ninety-four (57%) patients required Intensive Care Unit (ICU) level of care on admission. Average duration of ICU stay was 7.3 days (range 1–96 days).

The etiology of AKI was multifactorial in several patients [Figure 1]. Sixty patients (36%) were diagnosed with puerperal sepsis and 4% of cases were classified as septic abortion. Of patients with pre-eclampsia and eclampsia, 26% of patients had concomitant HELLP syndrome ($n = 27$) and 9.7% of cases were diagnosed with eclampsia ($n = 9$).

In terms of renal manifestations, 76% of the patients were diagnosed with AKI at the time of admission and the remaining patients developed AKI during the course of hospital stay. Oliguria, defined as u/o <0.5 ml/kg/h \times 6 h, or anuria, was seen in 45% of cases. Mean S.cr on admission was 3.7 mg/dl. Distribution of PRAKI as per RIFLE criteria is described in Table 1. RRT (AKI-RRT group) was initiated in 49 (30%) patients in the form of intermittent hemodialysis or slow low-efficiency dialysis in 38 (77%) patients. The average duration of RRT was 11 days.

Outcomes of PRAKI in relationship to RIFLE criteria are outlined in Table 1. The incidences of biopsy-proven CN and long-term RRT were 4.8% and 1.8%, respectively. Of the patients with CN, partial CN was seen in five patients and complete CN was seen in three patients. Biopsy

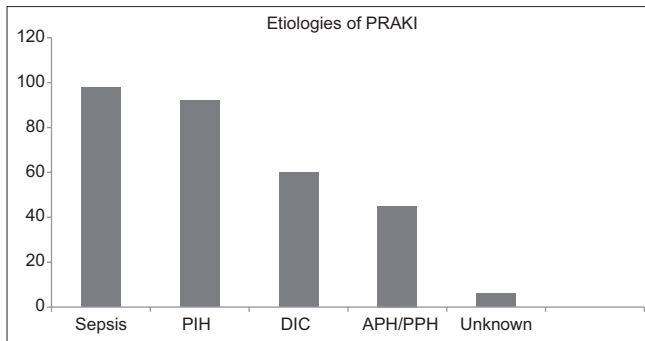


Figure 1: Etiologies of pregnancy-related acute kidney injury. Y axis: number (n) and X axis: etiologies. Sepsis: Majority cases of sepsis were proven or suspected bacterial sepsis. Incidence of septic abortion was 4%. Rare causes included systemic lupus erythematosus and hemolytic uremic syndrome. Acute fatty liver of pregnancy was seen in four cases

diagnosis of patients with persistent proteinuria (n = 6) included the following: membranoproliferative glomerulonephritis (n = 2), systemic lupus erythematosus, focal segmental glomerulosclerosis, membranous nephropathy, and mesangioproliferative glomerulonephritis (n = 1 each).

Maternal mortality was 20% (n = 33). Mortality with respect to RIFLE criteria is mentioned in Table 1, and its etiology is outlined in Table 2. With respect to pregnancy outcomes, 41 patients (24.8%) required lower section cesarean section. Fetal outcomes are outlined in Table 3.

In a univariate analysis, factors significantly associated with maternal mortality included hypotension and shock, hemorrhage requiring >5 units packed red blood cells, oliguria, sepsis, total bilirubin >5 mg/dl, requirement for RRT, and RIFLE “Loss” category.

Discussion

We report the lowest frequency of PRAKI of all the series from Indian subcontinent. Goplani *et al.* and Najjar *et al.* reported 9% and 7% incidence of PRAKI, respectively, in their series.^[3,5] Hassan *et al.*^[13] from Pakistan reported a substantially higher incidence of PRAKI (30%) in their series. While there is no standardized definition for PRAKI, it is well established that an S.cr value >0.8 mg/dl or UP/cr ratio >300 mg in pregnancy is considered as renal dysfunction.^[14] Other authors have utilized arbitrary S.cr values >1.5 mg/dl or 2 mg/dl, which can lead to under diagnosis of PRAKI, while early referrals to our institution and better provision of antenatal care may have contributed to lower incidence of PRAKI in our series.

RIFLE criteria have been utilized in contemporary PRAKI literature for classification of this entity and

Table 1: Division and outcomes of pregnancy-related acute kidney injury based on RIFLE criteria

	n (%)#	Recovered (%)*	Expired* (%)
Risk	36 (22)	29 (81)	7 (19)
Injury	60 (36)	45 (75)	10 (25)
Failure	57 (34)	46 (81)	10 (19)
Loss	09 (5)	03 (33)	06 (66)
ESRD	03 (2)	0	0

#Percentage calculated considering the total cohort of PRAKI patients (n=165), *Percentage calculated considering patients within each RIFLE category as the denominator. PRAKI: Pregnancy-related acute kidney injury, ESRD: End-stage renal disease, RIFLE: Risk, Injury, Failure, Loss of function and End-stage renal disease

Table 2: Causes of death (n=33)

Cause	Number
Sepsis	24
Bacterial sepsis	18
Hemagglutinin type 1 and neuraminidase type 1 influenza virus	2
Mucormycosis	2
Dengue/malaria	1 each
Antepartum hemorrhage	1
Postpartum hemorrhage	1
Antiphospholipid antibody syndrome	1

Table 3: Fetal outcomes of pregnancy

Birth weight (in g)	Number of deliveries
500-1500	42
1501-2500	81
2001-3500	30
>3500	2
Perinatal outcomes	
Abortions	12
Preterm	89
Intrauterine death	36
Stillbirth	28

prognostication. While majority of our patients were classified into “Injury” and “Failure” categories, in another study of dialysis-dependent PRAKI patients, predictably a higher prevalence of “Loss” and “Failure” stages^[15] was noted, whereas Bentata *et al.* noted the presence of “Risk” category in 50% patients with complete recovery of renal function in their cohort.^[16] These studies as well as other studies indicate that the severity of renal failure in PRAKI correlates negatively with renal recovery.^[17-19,20] More studies are required to explore the potential of RIFLE criteria to better define and classify this entity.

As noted in other series,^[21-23] majority of PRAKI was observed in postpartum period or third trimester, and in primigravidas, a group known to be at high-risk for preeclampsia and eclampsia.^[24,25] Similar to our cohort, sepsis contributed 30–60% cases of PRAKI in other series from Indian subcontinent, in contrast to 11% in Western literature.^[7] We noted a low incidence of septic abortions

in contrast to a higher incidence (12–50%) in some parts of India (12–50%) [Table 4].^[3,21] A high incidence of puerperal sepsis highlights the need for improving the quality of antenatal and perinatal care. In literature, the contribution of pre-eclampsia and eclampsia to PRAKI is variable, (14–86% of PRAKI), and it is reported that the incidence of AKI in preeclampsia is 1–8.9%, while in HELLP syndrome, it is around 8–15% with varying severity of renal dysfunction.^[26,27]

The overall incidence of AKI-RRT in our study (30%) is lower than those reported in other Indian subcontinent series (60–94%).^[3,18,21] The lower percentage of AKI-RRT in our series could be related to early detection of AKI either related to the criteria used for diagnosis or early referral to our center, leading to the earlier implementation of treatment. In contrast, Hildebrand *et al.*^[22] report a much lower incidence of AKI-RRT of 1 in 10,000 deliveries from Canadian database explained by differences in socio-economic conditions. A large variability has been observed in the percentage of patients requiring long-term RRT, ranging from 0%^[28] to 20–25%.^[6,23] In our cohort, a very small percentage of patients required long-term RRT, attributable to a low incidence of CN and severity of AKI in comparison to other studies and early and aggressive management of PRAKI.

The mortality rate observed in our series (20%) is similar to those found in contemporary series from India and other developing countries;^[3,7,21] however, it is higher than those noted in Western series.^[7] Of note, none of the patients with purely pregnancy-induced hypertension (PIH) or HELLP died, similar to findings noted by several other authors.^[27,28] It is evident that sepsis, severe hemorrhage, oliguria as well as AKI-RRT imply poor prognosis, findings which are consistent with reported determinants of maternal morbidity and mortality.^[16] In terms of perinatal outcomes, our findings are in concordance with other authors noting 26–38% of perinatal mortality and 66% incidence of low birth weight in women with PIH and AKI.^[25,27,28]

The strengths of our paper include a large sample size, availability of clinical data and reasonable length of follow-up with minimal patient attrition. Our paper highlights the vastly different characteristics of PRAKI in

developing and developed nations, as well as regional disparities within India, which have a direct bearing on the long-term outcomes of this entity. Our limitations include lack of information regarding hemodynamic monitoring in our ICU and impact of conservative treatment measures on study outcomes as well as lack of a control group, which could have helped to define risk factors for the development of PRAKI.

Conclusion

PRAKI remains a challenging health issue in developing countries. Further improvements in antenatal and perinatal care have the potential to improve maternal and fetal outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Table 4: Cause of sepsis

Causes	Number
Puerperal sepsis	60
Urinary tract infection	12
Pulmonary	9
Septic abortion	6
Mucormycosis	2
Unknown	9

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