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Original Research Article

Management and outcome assessment of pregnancy-related acute kidney injury in Western India: a single centred, prospective, observational study

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ABSTRACT

Background: Pregnancy-related acute kidney injury (PRAKI) remains a large public health problem, with decreasing incidences in developing countries like India. However, some single centred studies from United States and Canada revealed an increasing incidence of PRAKI. This increase could be due to higher rates of hypertensive disorders of pregnancy.
Methods: To assess the management and outcome of PRAKI. In this prospective, observational study, total 1021 cases of acute renal failure were observed.
Results: 96 (9.4%) were of obstetric origin and enrolled as per inclusion criteria. Regarding management of PRAKI, 78 out of 96 (81.25%) required haemodialysis. 67 (69.79%) among them were managed with intermittent haemodialysis (IHD) while 10 (10.41%) who had hypotension at presentation were dialysed with slow, low efficiency dialysis (SLED). Continuous renal replacement therapy (CRRT) was done in 1 (10.4%) patient. Maternal mortality in this PRAKI study was 19 of 96 patients (19.79%). Sepsis accounted for 52.63% of deaths. Foetal death was observed in 58 out of 96 patients (60.41%) comprising of intrauterine death in 55 (55.29%) and abortion in 3 (3.13%) patients. 38 of 96 (39.58%) patients gave birth to live born child out of which 27 were at full term and 11 were preterm.
Conclusions: In order to avoid further increase in PRAKI in India, treating obstetrician should remain aware of management and outcome of PRAKI. The better awareness of diagnosis and management protocols will ultimately lead to further reduction in prevalence of PRAKI in our country.

Keywords: Pregnancy-related acute kidney injury, Maternal mortality, Foetal mortality, Haemodialysis

INTRODUCTION

One of the most life-threatening complications of pregnancy is acute renal failure which leads to poor foetal and maternal outcome. It is called as pregnancy related acute kidney injury (PRAKI) with incidence of 1 in 20000 pregnancies in developed countries.[1] In developing countries like India, it is 1 in 50 pregnancies.[2] Rapid reduction in post-abortal sepsis and improved care of hypertension in pregnancy could have contributed in rapid reduction of incidence of PRAKI in developed countries. Septic abortions, poor follow up of patient with pregnancy, limited screening of pregnant patient with hypertensive complications and late referral to specialized treatment centres are responsible for high incidence of PRAKI in developing coutries.[3]

There was reduction in PRAKI incidence in developed countries over the last 60 years from 1 in 3000 in the mid-20th century to 1 in 20,000.[4] But in developing

countries, PRAKI contributes to almost 25% of referrals to dialysis centre.[5] India has PRAKI incidence ranging from 4.3% to 14.5%.[6,7] Septic abortion as a cause of PRAKI decreased from 33.3% in 1980-1985 to 6.3% in 1989-1997; however, it still remains the most common cause of PRAKI in developing countries.[8] PRAKI contributed 15 to 20 per cent among all cases of acute renal failure in developing countries.[4,5] The prevalence of obstetric ARF among all cases of ARF decreased from 14.5% in the 1980s to 7-10% in the 2010-15.[6-11] All the aetiologies that cause ARF in non-pregnant patient can cause ARF in pregnant patient like volume depletion, haemorrhage, sepsis in addition to pregnancy specific aetiologies like HELLP syndrome, acute fatty liver of pregnancy, thrombotic microangiopathy.[3]

The diagnosis of acute kidney injury in pregnancy is based on the serum creatinine increase.[9] The causes of obstetric ARF can be divided into three groups based on the duration of pregnancy viz, first half, second half and postpartum ARF. In first half, septic abortion contributed maximum in incidence of PRAKI while preeclampsia and antepartum haemorrhage (APH) are one of the commonest causes during second half of pregnancy. In the third trimester, the differential diagnosis is more challenging for the obstetrician and the nephrologist. Postpartum haemorrhage and puerperal sepsis are responsible for postpartum ARF.

Diagnosis and management of PRAKI does not differ a lot as per the geographical region or over different time frame. Only difference is the availability of resources required for diagnosis and management. In developing countries like India, many such cases are being referred to our tertiary care centre and mostly they belong to lower to middle socioeconomic class. Early diagnosis by primary/secondary centres and management by tertiary care centres with good infrastructure, updated equipment and trained doctors will not only reduce the prevalence of pregnancy associated acute kidney injury in our country but also improves the overall of maternal and foetal outcome. Simultaneously, awareness of this complication of pregnancy to treating doctors and other official stakeholders will help in managing necessary resources. Among the data available on PRAKI, there are very few studies in India which will focus exclusively on management and outcome of PRAKI. And this outcome analysis will help Government to measure the standard of Obstetric health care in India. Hence, the objective of our study was to conduct an observational study of assessment of management and outcome of pregnancy-related acute kidney injury in Western India.

METHODS

This was the prospective, observational study conducted at Institute of Kidney Diseases and Research Centre, Ahmedabad which is super speciality care centre from January 2014 to December 2015.

Acute Kidney Injury (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 post-delivery). During this study period, total 1021 patients were admitted to the hospital with acute renal failure due to various etiology. Out of which, 96 patients were due to renal failure from obstetric origin and included in our study with convenience sampling method.

The study protocol was approved by the institutional ethics committee and included a detailed patient information brochure. Informed consent was obtained from all participants or their next of kin. Pregnant patients who were not having history of renal disease previously and developed acute renal failure as evident by oliguria (urine output <400 ml/day) or rising azotaemia in presence of normal urine output were included in this study. Such 96 enrolled patients were treated and prospectively studied with respect to their history, clinical features, laboratory parameters, precipitating factors for acute renal failure, its complications, maternal and foetal outcome, and renal outcome at 3 months of discharge.

Detailed history, clinical examination, investigation, management and follow up were done according to proforma of case report form. Each patient underwent complete obstetric examination and removal of products of conception was done as and when required. If the initial event leading to ARF began outside the hospital, the information was collected from the patient and her immediate attendants and via medical referral records and telephone calls to the referring doctors whenever possible. Details of obstetric, medical, and surgical management—including the need for blood transfusion, dialysis, and intensive care—were recorded. For haemodialysis, access was obtained either by femoral or right internal jugular vein.

All details were recorded in a structured format in Microsoft excel 2010. Continuous variables were expressed as mean+SD whereas categorical variables were expressed in absolute numbers or percentages.

RESULTS

During our study period, total 1021 cases of acute renal failure were observed at our institute out of which 96 (9.4%) were of obstetric origin and enrolled in study as per inclusion criteria. The mean age of patients with obstetric ARF in present study is 26.21 years. Youngest patient was 19 years old and eldest was 38 years old. The maximum incidence of obstetric ARF was found in the age group of 24-29 years (53.13%) and it was least in patients above 35 years (3.13%) (Table 1).

We came across 27 (28.13%) primigravida patients and 69 (71.88%) patients as multigravida (Table 2). In our study of 96 patients, 17 patients (17.7%) presented in early

pregnancy while 44 patients (45.83%) presented in late pregnancy and 35 patients (36.46%) presented in postpartum period (Table 3).

Table 1: Distribution of patients with obstetric ARF in different age groups.

Age distributions (in years)	No. of patients (n=96)	%
18-23	23	23.95
24-29	51	53.13
30-35	19	19.79
36-38	3	3.13

Table 2: Parity distribution.

Gravida	No. of patients	%
Primigravida	27	28.13
Multigravida	69	71.88

Table 3: Pregnancy status at the time of presentation.

Pregnancy status	No. of patients	%
Early pregnancy (1^{st} and 2^{nd} trimester)	17	17.70
Late pregnancy (3^{rd} trimester)	44	45.83
Postpartum	35	36.46

Table 4: Management with dialysis.

Management	No. of patients	%
Conservative	18	18.75
IHD	67	69.79
SLED	10	10.41
CRRT	1	1.04

(IHD – Intermittent Haemodialysis, SLED – Slow, Low efficiency dialysis, CRRT – Continuous Renal Replacement Therapy)

Table 5: Operative management.

Operation	No. of patients (32 out of 96)	%
Retained products of conception evacuation	29	30.21
Resuturing of wound	1	1.04
Obstetric hysterectomy	2	2.08

In the present study, 78 out of 96 (81.25%) required haemodialysis. 67 (69.79%) among them were managed with intermittent haemodialysis (IHD) while 10 (10.41%) who had hypotension at presentation were dialysed with slow, low efficiency dialysis (SLED). Continuous renal replacement therapy (CRRT) was done in 1 (10.4%) patient with hypotension requiring vasopressor support (Table 4). Out of 77 patients who were alive, 42 patients (43.75%) had complete recovery of renal function. 16 (16.67%) patients had partial recovery i.e. they became dialysis independent and average requirement of haemodialysis was 10.5 per patient over 20-30 days. 19 (19.79%) patients had no recovery at the end of 3 months follow up (Table 6).

Table 6: Renal outcome.

Renal Outcome	No. of patients (77 out of 96)	%
Complete recovery	42	43.75
Partial recovery (dialysis independent)	16	16.67
No recovery	19	19.79

Table 7: Immediate cause of maternal death.

Sr. no.	Causes	No. of patients (n= 19)	%
1	Septic shock	10	52.63
1a	Postabortal	2	10.5
1b	Puerperal	8	42.1
2	**DIC**	8	42.1
2a	DIC-HELLP	5	26.3
2b	DIC-Haemorrhage	2	10.5
2c	DIC-Malaria (falciparum)	1	5.3
3	**Pulmonary oedema**	1	5.3

Table 8: Foetal outcome.

Sr. no.	Foetal outcome	No. of patients	%
1	Alive	38	39.58
1a	Full term	27	28.12
1b	Preterm	11	11.46
2	Foetal Death	58	60.41
2a	IUD	55	57.29
2b	Abortion	03	3.13

In the present study, maternal mortality was present in 19 of 96 patients (19.79%). All patients who expired had mortality before renal functional recovery. Sepsis accounted for 52.63% of deaths. 2 patients had sepsis following abortion and 8 patients had due to puerperal infection. 8 patients (42.1%) expired due to DIC. HELLP was most common cause leading to mortality due to DIC (26.3%) and DIC occurred following haemorrhage in 2 (10.5%) and following falciparum malaria in 1 (5.3%) patients. One patient expired due to pulmonary oedema (Table 7). In present study, foetal death was observed in 58 out of 96 patients (60.41%) comprising of intrauterine death in 55 (55.29%) and abortion in 3 (3.13%) patients.

38 of 96 (39.58%) patients gave birth to live born child out of which 27 were at full term and 11 were preterm (Table 8). In the present study, puerperal sepsis was observed in 63.54% of patients. Out of these 61 patients, more than half (55.74%) had complete recovery and 11.47 % had partial recovery while 18.03% were dialysis dependent at 3 months of follow up. Maternal mortality was observed in 9 (14.29%) patients. Patients with PPH had relatively better renal outcome in the form of complete recovery in 60% and renal impairment in 26.67% of patients. Maternal mortality was observed in 2 (13.33%) patients. Antepartum haemorrhage was a precipitating event in 21.86% of patients and only 4 of 21 (19.04%) of these patients had complete recovery while 14 (66.58%) had some form of renal impairment. 3 (14.29%) of patients expired and foetal mortality was observed in 17 (80.95%) of patients which was worst excluding patients with CKD. Hence, APH carried a worse renal and foetal outcome. Fifty percent of patients with preeclampsia / eclampsia had renal impairment while 6 (27.27%) patients had complete recovery. 5 (22.73%) of patients expired. Foetal mortality was seen in 17 (77.27%) patients. Preeclampsia/eclampsia was associated with poor renal, maternal and foetal outcome in our study. Presence of HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) further increased the severity and lead to poor renal, maternal and foetal outcome as evident from the table 9. Interestingly, 7 patients with CKD presented for the first time with ARF in pregnancy and had poor foetal outcome as no patient could successfully delivered a live child. One patient expired due to sepsis. Two patients who presented late near term showed partial recovery i.e. they became independent of dialysis at 3 months of follow up after termination of pregnancy (Table 9).

Table 9: Comparison of etiological factors and renal outcomes in patients with and without renal cortical necrosis and with maternal mortality.

Etiological factor	Incidence n=96	Complete recover	Partial recovery	No recovery	Maternal mortality
Postabortal sepsis (6)	6.25%	2 (33.33%)	1 (16.67%)	1 (16.67%)	2 (33.33%)
Puerperal sepsis (61)	63.54%	34 (55.74%)	7 (11.47%)	11 (18.03%)	9 (14.75%)
APH (21)	21.86%	4 (19.04%)	8 (38.1%)	6 (28.57%)	3 (14.29%)
PPH (15)	15.63%	9 (60%)	2 (13.33%)	2 (13.33%)	2 (13.33%)
Preeclampsia / Eclampsia (22)	22.92%	6 (27.27%)	5 (22.73%)	6 (27.27%)	5 (22.73%)
HELLP (14)	14.58%	4 (28.57%)	3 (21.43%)	3 (21.43%)	4 (28.57%)
CKD (7)	7.29%	0	2 (28.57%)	5 (71.43%)	1 (14.29%)

(APH – Antepartum Haemorrhage, PPH – Postpartum Haemorrhage, HELLP - Haemolysis, Elevated Liver Enzymes, Low platelet count, CKD – Chronic Kidney Disease).

Table 10: Comparison of laboratory parameters in patients with and without renal recovery.

Lab parameters	CR (N=42)	PR (N=16)	NR (N=19)
Haemoglobin <8 gm%	19 (45.24%)	6 (37.5%)	3 (15.79%)
Thrombocytopenia (PLT <1 lac)	21 (50%)	10 (62.5%)	9 (47.37%)
Lactate dehydrogenase (>1000)	14 (33.33%)	11 (68.75%)	7 (36.84%)
Fibrinogen (<200)	4 (9.52%)	4 (26.67%)	4 (21.05%)
Creatinine (>4.0 mg/dL)	24 (57.14%)	14 (87.5%)	15 (78.94%)

CR: complete recovery; PR: partial recovery; NR: no recovery.

We encountered anaemia (Hb <8.0 gm%) in 25 of 58 (43.10%) patients either with complete recovery or with partial recovery (independent of dialysis at 3 months) while it was present in 3 of 19 (15.79%) patients without recovery. High serum creatinine (>4 mg/ dL) was associated with poor renal outcome, as it was noted in 82.86% of patients with renal impairment against 57.14% of patients with complete recovery (Table 10).

DISCUSSION

Pregnancy-related acute renal failure is usually a consequence of obstetric complications, and therefore prevention measures should be directed at addressing the lacunae of existing maternity care.[10,11]

The mean age of patient in present study was 26.21 years which was in accordance with studies from West India by Pahwa et al (26.7 years), Godara et al (26.4 years), Goplani et al (25.6 years). While it was higher in studies from North India by Krishna et al (28.85%) and Nazar et al (28.94%).[12-16] This difference in region could be due to completion of fertility early due to lower age of marriage. In the present study, 27 (28.13%) patients were primigravida while 69 (71.88%) patients were multigravida. This is in accordance with study by Najar et

al, where 30% cases were primigravida and 70% were multigravida while Krishna et al16 found 20.4% cases of primigravida and 79.6% of multigravida.[10]

Maximum patients in our study group were presented in late pregnancy. In a study by Krishna et al 15.3% of patients developed ARF in 1st trimester, 28.57% developed ARF in 2nd trimester while 56.12% of patients were in 3rd trimester. In a study by Gopalkrishnan et al, most of the patients (68%) presented in postpartum period.[17] In contrast to our observations, earlier studies by Chugh et al in 1976 of 72 patients, 43 patients (59.7%) developed ARF in early pregnancy while 29 (40.35%) patients developed ARF in late pregnancy.[18] This difference could be due to high number of ARF due to abortion during those days.

Rao et al from United States quotes that there are limited data on the timing of initiation, duration of therapy, or choice of modality of renal replacement therapy in Pr-AKI, thus the dialysis prescription needs to be individualized. Like dialysis management in pregnant women with end-stage renal disease, longer and more frequent dialysis sessions should be considered to avoid hypotension, to restore electrolyte homeostasis, and to adequately remove uremic toxins.[19]

During case management in our study, Intermittent haemodialysis (IHD) was most commonly used followed by Slow, low efficiency dialysis (SLED) method. Continuous renal replacement therapy (CRRT) was done in patient with hypotension requiring vasopressor support. In a study by Gopalkrishnan et al, most of the patients 96 of 130 (73.85%) needed haemodialysis while rest 26.15% patients were managed conservatively.[17] Similarly, Nazar et al also observed that almost 55% patients required haemodialysis and 40% were managed conservatively.[13,16] 46% of patients who were hypotensive were offered SLED or CRRT. Operative management was required in 32 of 96 patients which included evacuation of products of conception in majority of cases followed by obstetric hysterectomy and resuturing of wound. Krishna et al observed that evacuation of retained products was required in 18.37% of patients.[12] Obstetric hysterectomy and cervical tear repair was needed in 22.5% and 2.5% of patients in a study by Nazar et al.[16]

Out of 77 patients who were alive, 42 patients had complete recovery of renal function. 16 patients had partial recovery i.e. they became dialysis independent and 19 patients had no recovery at the end of three months follow up. Similar observations were reported by Pahwa et al, where 40.7% had complete recovery, 22.2% had partial recovery and 18.5% patients did not recovered renal function.[15] Similar observations were noted by Gopalkrishnan et al, where 56% of patients had complete recovery and 36% had persistent renal failure at three months.[17] In contrast, Nazar et al, showed that only 1 patient out of 40 remained dialysis dependent and two had partial recovery while rest of the patients recovered completely.[16] This difference in renal functional recovery could be due to the difference in the etiological factors and multiple etiological factors leading to acute renal failure as observed in present study. Septic abortion accounted for half of cases of ARF in study by Nazar et al whereas it is responsible for only 6.25% of ARF cases in present study.[10]

In the present study, maternal mortality was present in 19 of 96 patients (19.79%). This result is similar to the maternal mortality observed by other investigators from different parts of India (Table 11). From table 11, it is evident that maternal mortality due to acute renal failure in pregnancy has decline from 55% in 1976 to 19.79% in present study and 18-20% in 2008-2015 from other studies. Sepsis and disseminated intravascular coagulation (DIC) accounted for maximum deaths. HELLP was most common cause leading to mortality due to DIC followed by haemorrhage and infection of falciparum malaria. This is in accordance with study by Goplani et al in which sepsis accounted for 61.53% of death.[14] Krishna et al in their study also showed that relative risk of mortality associated with sepsis was 1.7 Similar observations were made by Prakash et al that sepsis accounted for 50% of mortality and in a study by Selcuk et al septic shock was main reason for death in 61% of expired patients.[20,21]

Foetal death was observed in 58 out of 96 patients (60.41%) comprising of intrauterine death in 55 and abortion in 3 patients. 38 of 96 (39.58%) patients gave birth to live born child out of which 27 were at full term and 11 were preterm. Krishna et al, observed foetal mortality in 46.94%, preterm delivery in 9.18% and full term delivery in 43.8% of patients.[12] The high foetal mortality may be due to poor antenatal care, late referral of high risk cases, ignorance and lack of medical facilities.

Rao et al mentioned that the successful management of Pr-AKI requires a multidisciplinary approach with close collaboration among nephrologists, obstetricians, intensivists, and other team members. The identification of the underlying etiology of Pr-AKI is crucial in its proper management.19 We had come across puerperal sepsis as most common etiological factor for PRAKI. Goplani et al also found that puerperal sepsis was most common aetiology for obstetric ARF.[14] Though puerperal sepsis is the most common etiological factor leading to obstetric ARF, a better renal and maternal outcome was observed in the present study. This could be due to the early institution of antibiotic therapy in this group of patient. Patients with PPH had relatively better renal outcome in the form of complete recovery in 60% and renal impairment in 26.67% of patients. Maternal mortality was observed in 2 (13.33%) patients. Similar outcomes were observed by Goplani et al, with 17.64% of maternal mortality.[14] Quick replacement of blood products even before referral to tertiary centre may have resulted in better outcome. Antepartum haemorrhage was a precipitating event in 21.86% of patients and only 4 of 21 (19.04%) of these patients had complete recovery and 14 (66.58%) of patients had some

form of renal impairment. Hence, APH carried a worse renal and foetal outcome. Goplani et al also observed comparable maternal mortality (20%) and foetal mortality (80%) in patients with APH.[14] This could be due to the exsanguination of placenta causing foetal hypoxia and foetal mortality and release of tissue factor in maternal circulation leading to DIC. Fifty percent of patients with preeclampsia / eclampsia had renal impairment while 6 (27.27%) patients had complete recovery. 5 (22.73%) of patients expired. Foetal mortality was seen in 17 (77.27%) patients. Preeclampsia/eclampsia was associated with poor renal, maternal and foetal outcome in our study. This is in accordance with the study by Goplani et al in which 15% maternal mortality and 60% of foetal loss was observed with preeclampsia/ eclampsia.[14] Presence of HELLP further increased the severity and lead to poor renal, maternal and foetal outcome as evident from the table. This could be due to the late referral and underdiagnoses of such high risk cases. As per Rao et al preeclampsia occurs in 2% to 8% of pregnancies, and is most commonly in the second and third trimester period but can occur in the postpartum period in up to 5% of cases.[22,23] Interestingly, a history of recovered AKI unrelated to pregnancy is associated with a higher risk of preeclampsia in future pregnancies.[24] Although preeclampsia is associated with a 30% to 40% reduction in renal blood flow and glomerular filtration rate compared with a normal pregnancy, PRAKI is an uncommon manifestation (1%), unless preeclampsia is severe or associated with the HELLP syndrome.[25] The HELLP syndrome, associated with PRAKI in 7% to 36% of cases, is classified as a preeclampsia/ eclampsia continuum, even though 20% of cases do not have antecedent hypertension or proteinuria.[26]

Interestingly, seven patients with CKD presented for the first time with ARF in pregnancy and had poor foetal outcome as no patient could successfully delivered a live child.

Anaemia (Hb <8.0 gm%) was present in 25 of 58 patients either with complete recovery or with partial recovery (independent of dialysis at 3 months) while it was present in 3 of 19 patients without recovery. Anaemia did not predict the renal recovery as it was the treated with blood transfusion. Thrombocytopenia was equally distributed which could be due to by chance as it was associated with sepsis which was the most common reason for obstetric ARF. Hence the presence of thrombocytopenia had no correlation with renal recovery. In contrast, Gopalkrishnan et al in their study noted that mean low platelet count at presentation predicted the progression to chronic kidney disease.[17] There was no correlation between serum LDH levels and renal outcome as it was nonspecific marker apart from cases of HUS where it was related with severity of disease. Decreased levels of plasma fibrinogen were observed in patients with renal impairment than patients having complete recovery. High serum creatinine (>4 mg/ dL) was associated with poor renal outcome, as it was noted in 82.86% of patients with renal impairment against 57.14% of patients with complete recovery. Similar results were observed in a study by Gopalkrishnan et al, in which higher peak serum creatinine was observed to predict progression to chronic kidney disease.[17]

We had certain limitations in our study like the multivariate analysis among etiological and laboratory parameters with that of overall outcome of PRAKI was not done.

CONCLUSION

To conclude, there might have a gap between assessment and implementation of study techniques. Step must be taken to rectify gap between assessment and implementation. The results of a study on medical students showed that attending study skill workshops and learning related abilities can empower the students in the areas of selecting the main idea, study aids, information processing, self-testing, and use of test strategies.19, 20 However, teaching self-regulation strategies and practicing them in class can create opportunities that help the students manage and monitor their learning.21

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