Original Research Article

Spectrum of Pregnancy Related Renal Cortical Necrosis: A Study From Western India

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Abstract

Background: Pregnancy complicated by acute kidney injury is associated with higher morbidity and mortality in developing countries. The occurrence of renal cortical necrosis (RCN) in pregnancy related acute kidney injury may lead to grave renal prognosis. **Objectives:** This study is to analyse the risk factors that lead to acute cortical necrosis in all cases of pregnancy related acute kidney injury presenting in a tertiary care institute in Western India from January 2021 to July 2021, and assess the renal outcomes. **Materials and Methods:** Patients with pregnancy related acute kidney injury suspected to have a clinical profile of acute cortical necrosis, were subjected to histopathological and/or radiological examination for confirmed diagnosis. 4 patients were included in this case series. The etiology of the cases leading to cortical necrosis were analysed. Their prognosis was studied in terms of patient and renal outcomes for a period of 3 months postpartum. **Results:** The patients median age was 31 years. The most common aetiology was postpartum haemorrhage seen in 3 cases. The presence of postpartum thrombotic microangiopathy seen in one case is an important cause of RCN. Three of our four patients (75%) showed diffuse cortical necrosis. All needed renal replacement therapy at presentation. Two patients (50%) showed partial recovery of renal functions and became dialysis independent at 3 months postpartum.**Conclusions:** This study emphasises the need for early diagnosis and timely institution of appropriate management in cases of obstetric AKI with renal cortical necrosis to curtail the morbidity and mortality in young women.

Keywords: Renal Cortical Necrosis; Acute Kidney Injury; Postpartum Haemorrhage; Thrombotic Microangiopathy; Renal Replacement Therapy.

Introduction

Pregnancy complicated by acute kidney injury is associated with higher morbidity and mortality in developing countries. The occurrence of renal cortical necrosis in pregnancy related acute kidney injury (AKI) may lead to grave renal prognosis[1,2]. Renal cortical necrosis can be diffuse and generalised or patchy and focal. It is the ischemic destruction of the glomerular tissue due to significantly reduced blood supply compromising renal arterial perfusion[3].

The incidence of pregnancy related acute cortical necrosis has declined to 1-2%[4] in developed countries, while it continues to be as high as 5-7%[5] in developing countries. The aetiological causes of RCN are diverse. RCN is most commonly associated with obstetric causes such as postpartum haemorrhage (PPH), pre- eclampsia in 60-70% cases[6,7], while rest 20-30% are seen secondary to non-obstetric causes, like snake bite[8] and hyperacute renal allograft rejection[5].The gold standard diagnosis of RCN is done by histopathological examination of the renal biopsy tissue[9].However, being an invasive procedure, it warrants normal coagulation profile and hemodynamic stability. Other alternative non-invasive options for diagnosis of RCN are functional imaging tests like CT scan and MRI scan. While non contrast CT picks cortical calcifications, contrast CT scan shows hypo-attenuated subcapsular rim of renal cortex[10].This case series is to share our centre experience of obstetric related RCN seen in pregnant females presenting with acute kidney injury, their etiology and their renal outcomes.

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Materials and Methods

This hospital-based retrospective series of 4 adult cases was conducted in the Department of nephrology at a tertiary care referral centre in Western India from January 2021 to July 2021 on patients with RCN due to pregnancy-related complications. All cases who fulfilled the inclusion criteria were included. This study was approved by the relevant institutional ethics committee. All data on demographic details, obstetric history and clinical presentation and laboratory investigations were obtained from hospital records. Obstetric history included parity, history of antenatal follow-up, period of gestation, mode of delivery and peripartum complications. Maternal and fetal outcomes of pregnancy were noted. The etiology, the onset of acute kidney injury with respect to the period of gestation, the need for renal replacement therapy and its timing, and long-term renal outcomes in terms of dialysis dependency and kidney functions at three months post-partum were recorded. Anuria was defined as urine output <100ml in 24 hours and oliguria was <400ml in 24 hours.

For the confirmative diagnosis of RCN, kidney biopsy or functional imaging like contrast enhanced Computerised Tomography (CT) Scan was done. Renal biopsy was done in patients having anuria or oligo/anuria, dialysis dependent AKI or partial recovery from AKI for >4 weeks to look for RCN. The biopsy tissue was sent for light microscopy to delineate between patchy and diffuse nature of cortical necrosis. The lack of enhancement within the cortex of both the kidneys on imaging studies was diagnostic of RCN.

From 3 months postpartum, kidney function was evaluated by estimated glomerular filtration rate using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.

Inclusion Criteria: All female patients presenting with pregnancy-related AKI with clinical profile of cortical necrosis along with histological and/ or radiological evidence of cortical necrosis were included in the study.

Exclusion Criteria: Patients with comorbidities such as diabetes mellitus, hypertension, chronic kidney disease and renal transplant recipients were excluded from the analysis.

Definitions:

AKI in Pregnancy: The diagnosis of AKI in pregnancy based on any one of the three criteria: (a) serum creatinine >1 mg/dL, (b) oliguria >12 h duration, and (c) requirement for renal replacement therapy.

Postpartum AKI: AKI diagnosed from the time of delivery to six weeks post delivery

***Preeclampsia*:** Blood pressure reading >140/90 mm Hg diagnosed for the first time after 20 weeks of gestation with/ without 2+ proteinuria on dipstick.

Severe Preeclampsia: Association of severe arterial hypertension (systolic arterial pressure exceeding 160 mm Hg and diastolic arterial pressure exceeding 110 mm Hg) or proteinuria ≥5 g/L or ≥3 + or signs of visceral involvement (headaches, visual disturbances, epigastric, or right upper-quadrant pain).

Eclampsia: Presence of new-onset generalised tonic-clonic seizures in a woman with pre-eclampsia.

HELLP Syndrome: Combination of thrombocytopenia (<1 lac/cm), and hemolysis, and elevated liver enzymes.

Puerperal Sepsis: As per the World Health Organization definition – Any bacterial infection of the genital tract that occurs after the birth of a baby.

PPH: A blood loss of ≥500 mL after vaginal delivery or ≥1000 mL after cesarean delivery or as noted in the medical record by a care provider[2].

Postpartum Thrombotic Microangiopathy (TMA): Presence of autoimmune hemolytic syndrome (characterized by the presence of schistocytes, increased reticulocyte count, and raised lactate dehydrogenase), thrombocytopenia, and renal failure or evidence of TMA on a renal biopsy following pregnancy.

RCN: Clinical evidence of non-recovering AKI beyond four weeks with dialysis dependency along with histological/CT evidences of RCN i.e., the total ischemic necrosis of the entire elements (glomeruli, blood vessel, and tubule) of the affected area of renal cortex is a typical histological feature of RCN, while non contrast CT revealing cortical calcification and contrast enhanced CT scan revealing hypo attenuation of the subcapsular rim of renal cortex.

Renal Histology of RCN: Light microscopy: There is coagulative necrosis involving all tubular segments and glomeruli. Nuclei appear pale and pyknotic or may no longer be distinctly visible.

Renal Histology of RCN Secondary to TMA: Both tubules and glomeruli are necrotic with fibrin filling glomeruli and inter-lobular vessel, with early signs of injury like fibrin thrombi in the glomerular capillaries, fibrinoid necrosis of vessel walls may be seen. Immunofluorescence microscopy: No specific staining will be seen.

Complete Cortical Necrosis: Confluent global cortical destruction extending into the columns of Bertin. The thin rim of subcapsular and juxtamedullary tissue may be preserved. Irreversibility of renal function is the rule in complete cortical necrosis.

Patchy Cortical Necrosis: Contiguous areas of cortical necrosis involving one-third to half of the entire cortical tissue. This form has the potential for partial recovery of renal function to dialysis independency.

Outcomes: Patient outcomes were evaluated for mortality and renal outcomes.

Complete Recovery: Improvement of renal functions to serum creatinine to ≤1.0 mg/dL or to baseline within six weeks of onset of AKI.

Partial Recovery: Recovery of the renal functions of patient to dialysis independent state irrespective of serum creatinine levels.

No Recovery: Patient who had persistent anuria/ oligonuria and dialysis dependency for more than 4 weeks.

We analysed the data of 4 adult patients who were found to have obstetrical RCN from a period of 6 months from January 2021 to July 2021, for the etiological factors leading to RCN and its outcome.

Statistical Analysis

Normality of the continuous data was tested using Shapiro–Wilk test. Continuous data were presented in mean ± standard deviation, but in case non-normal data, median (interquartile range) was used and qualitative variables were expressed as percentage.

Results

The clinical characteristics and laboratory features of the 4 patients included in this study are summarised in Table 1 and 2. The mean age of the patients was 31 ± 4 years with a range of 28-35 years. All were multipara and had a single intrauterine gestation. One of the patients had a significant previous obstetric history in the form of a first trimester miscarriage. Two out of the 4 patients had gestational hypertension without proteinuria, detected around 34 weeks of gestation, necessitating treatment.

Mean period of gestation was 39 ± 0.2 weeks. Three patients underwent a Caesarean section due to obstetric indications, 2 due to previous LSCS and 1 due to non-progress of labour. One patient underwent Normal Vaginal delivery. All four patients (100%) delivered a healthy baby with an average birth weight of 2.75kgs, with an uneventful neonatal course. Two of the patients had significant postpartum haemorrhage, maximum blood loss being 2.2 Litres. The mean blood loss postpartum was 1350 ± 621.7 mL. One of the 2 patients having PPH developed hemodynamic instability necessitating inotropic support.

The mean time of presentation to the hospital from the time of delivery was 39 ± 15.27 hours. The mean peak serum creatinine levels were 6 ± 1.9 mg/dL. The main presenting symptoms were anuria and fluid overload in three of 4 patients while one had hypertensive emergency with pulmonary edema at presentation. The mean first 24-hour urinary volume was 142.5 ± 174.8 mL. All patients required Renal replacement therapy at presentation, of which two patients within first 24 hours of admission. Supportive treatment was required in 3 patients in the form of packed Red Blood Cell transfusions and Plasma Exchange in one patient P1. One patient (P3) was on ionotropic support and was given Slow Low Efficiency Dialysis. Diagnostic interventions and management are summarised in Table-3.

P1 had clinical and laboratory evidence of thrombotic microangiopathy. Her further work up for the cause of TMA was done. Anti-Complement Factor H Antibody levels were 73 (10-100) within normal range. Her genetic analysis sent subsequently revealed a missense mutation in Complement factor H. Two of the patients (50%) had postpartum haemorrhage and sepsis in one of the patients, while one patient (25%) had with history of gestational hypertension had pre- eclampsia and HELLP syndrome as the etiology, as evidenced by deranged transaminases and coagulopathy.

In view of non-recovering AKI, renal biopsy was performed in 3 patients after optimising of coagulation parameters. All three patients had evidence of ischemic cortical necrosis with thrombosis in arterioles and/or glomerular capillaries. It was diffuse involvement of the glomerular capillaries/ tubule, interstitium and vessels in two of the 3 patients, while patchy distribution of cortical necrosis involving less than 50% of the glomeruli in remaining one biopsy. One had additional features of glomerular capillary endotheliosis and fibrinoid necrosis in the arterioles, and double contours on capillary walls stained by JMS stain characteristic of thrombotic microangiopathy with acute interstitial nephritis, depicted in Figure 1 and 2. In one patient, contrast enhanced CT scan showed evidence of symmetrical non enhancing cortex confirming radiological evidence of RCN, as seen in Figure 3.

All four patients required renal replacement therapy at presentation (100%). One patient (P1) received a short duration of corticosteroids

in view of acute interstitial nephritis (AIN) on biopsy. Despite having diffuse cortical necrosis on biopsy, there was gradual partial recovery of renal function and became dialysis independent after 2 weeks. There was no mortality, however two patients (50%) remained dialysis dependent even at 3 months follow- up. One patient with biopsy proven patchy RCN also showed partial renal recovery and became dialysis independent. Patient outcomes in terms of mortality, morbidity in terms of renal outcome at 3 months follow up and fetal outcomes are summarised in Table-4.

Table 1: Clinical features of the study patients (P1-P4)

Parameter	P1	P2	P3	P4
Age (years)	35	27	28	34
Parity	Multipara	Multipara	Multipara	Multipara
Gestation age	39.2	39.4	38.2	38.5
Mode of delivery	LSCS	LSCS	FTNVD	LSCS
Presentation (hours)	48	60	24	24
Gestational hypertension	Present	Present	Absent	Present
Proteinuria	Absent	Absent	Absent	Absent
Pregnancy disorder	TMA	PPH	PPH	PE/ HELLP syndrome
Blood loss (mL)	600	2200	1700	900
Hemodynamic instability	-	-	+	-
First 24-hour Urinary volume (mL)	400	50	100	20

LSCS- Lower segment Caesarean section, FTNVD- Full term normal vaginal delivery, TMA- thrombotic microangiopathy; PPH- postpartum haemorrhage; PE- pre- eclampsia; HELLP – Haemolysis, elevated liver enzymes, low platelets.

Table 2: Laboratory parameters of the study patients (P1-P4)

Parameter	P1	P2	P3	P4
Hemoglobin (g/dL)	9.4	7.2	4.3	6.6
TLC (/cmm)	31,000	31,200	19,000	3290
Platelet count (/cmm)	85,000	98,000	1,80,000	50,000
Creatinine (mg/dL)	7.3	5.2	3.7	7.8
Serum LDH (U/L)	1718	214	3485	7862
Reticulocyte Count	2.5%	0.9%	0.9%	1.0%
Serum haptoglobulin (mg/dL)	<10	180	<10	338
Peripheral smear for schistocytes	3%	-	-	-
Total bilirubin (mg/dL)	0.6	0.5	0.6	1.9
ALT (U/L)	53	39	16	230
AST (U/L)	33	60	11	313
C3 level (mg/dL)	46	-	110	-
C4 level (mg/dL)	15	-	43	-
ANA	Negative	Negative	Negative	Negative
PT/INR	1.07	1.9	1.8	1.5
aPTT (seconds)	30	40	38	43
d- Dimer (mcg/mL)	4	4.48	3.2	1.0

LDH- lactate dehydrogenase; ALT- alanine transaminase; AST- aspartate aminotransferase;
C3- complement C3; C4- Complement C4; PT/INR- prothrombin time/ international normalised ratio; aPTT- activated partial thromboplastin time.

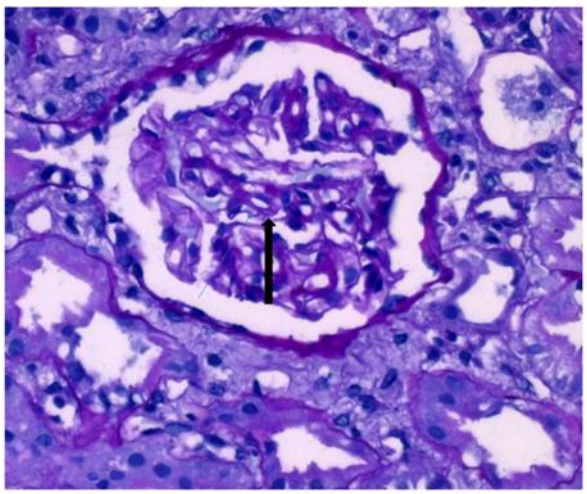

Fig. 1: Light microscopy showing glomerular capillary endotheliosis (black arrow) and fibrinoid necrosis in H & E stain (Hematoxylin and Eosin)

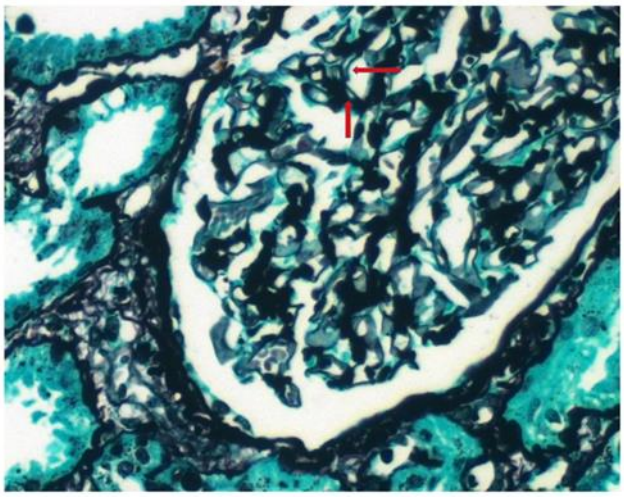

Fig. 2: Double contours in capillary walls (red arrows) on Jones Methanamine Silver stain confirming the diagnosis of thrombotic microangiopathy in pregnancy related AKI, seen in patient P1

Table 3: Diagnostic modalities used, pathological diagnosis and therapeutic management of the study patients (P1-P4)

Parameter	P1	P2	P3	P4
Procedure	Biopsy	CECT scan	Biopsy	Biopsy
RCN type	Patchy with TMA	Diffuse	Diffuse	Diffuse
RRT	+	+	+	+
PRBC transfusion	+	+	+	+
PLEX	+	-	-	-
Treatment	Steroids	-	Inotropic support	-

RCN- renal cortical necrosis; CECT- contrast enhanced Computerised Tomography; RRT- renal replacement therapy; PRBC- packed red blood cells; PLEX- plasma exchange.

Discussion

Renal cortical necrosis is an important cause of acute kidney injury occurring in the pregnant women, as it causes significant morbidity in terms of end stage renal disease in young women as well as mortality. The renal cortex undergoes ischemic destruction as a consequence of a significantly compromised renal arterial perfusion due to any of the vascular pathologies like spasm of the vessel, microvascular injury, or intravascular coagulation[3,5].RCN occurs in two peaks, the first peak in early infancy due to severe perinatal events or condition and the second peak occurs in women of childbearing age due to obstetric causes. Various etiological factors precipitate obstetric RCN such as postpartum haemorrhage (PPH) secondary to abruptio placentae, placenta praevia, HELLP syndrome, eclampsia, thrombotic microangiopathy, amniotic fluid embolism and puerperal sepsis and septic abortions, accounting for 60-70% of case[1,2,11] which has become extremely rare <2% in developed countries[12].

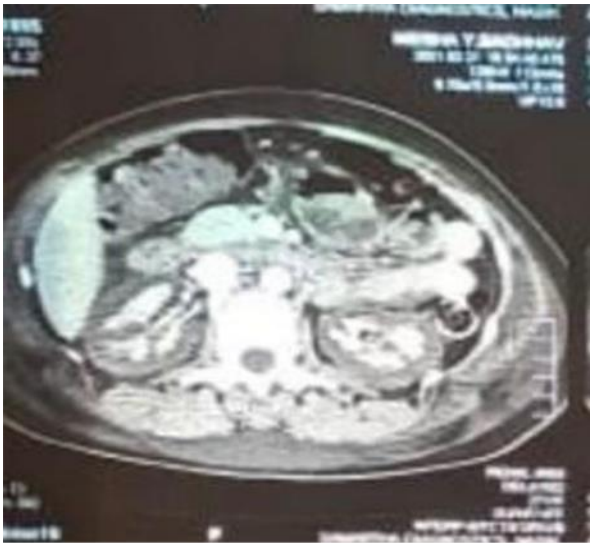

Fig. 3: CECT scan of patient P2 showing hypo-attenuated subcapsular rim of the renal cortex (red arrows), diagnostic of renal cortical necrosis

Over the years, the incidence of RCN is gradually decreasing from 17% to 2.4% in the developing countries cases[13]. This change has been the result of increased awareness of regular ante- natal check – ups, stringent laws preventing illegal and septic abortions and better medical care facilities helping early diagnosis and management of complications like pre-eclampsia. However, puerperal sepsis and septic abortions still continue to be a cause of concern, leading to increased morbidity and mortality in the peripartum period. Non-obstetric causes include extensive burns, snake bite[8], sepsis, haemolytic uremic syndrome[14], pancreatitis, extreme dehydration in infancy and childhood[15] and massive cholesterol emboli, with sepsis being the most common etiology accounting for 30-40%.

Renal cortical necrosis may be diffuse and generalised or focal and patchy in distribution. This distinction mainly helps predict renal prognosis as patients with patchy cortical necrosis often regain renal function over time, while diffuse cortical involvement progresses to dialysis dependent renal failure[5].In our study, twenty- five percent showed patchy involvement, while diffuse cortical necrosis was the pathology in 75% of the study population. The injury depends on the initial insult to a large extent. At times, the juxta-medullary glomeruli which constitute to 15-20%, may escape destruction even in diffuse ischemic necrosis and this nephron segment may play a role in the early functional recovery in these cases. In due course of time, the remaining healthy glomeruli undergo compensatory hypertrophy and at times, be instrumental in gradual renal recovery at a later stage[16]. This could be the possible explanation for one of our patients who showed partial recovery in a biopsy proven diffuse cortical necrosis and became dialysis independent after 8 weeks.

Table 4: Patient outcomes, renal outcomes and fetal outcomes of our patients

Parameter	P1	P2	P3	P4
Patient outcome	Discharge	Discharge	Discharge	Discharge
eGFR at discharge	36	DD	DD	DD
eGFR at 3 months follow-up	36	ESRD	ESRD	30
Renal outcomes	Partial recovery	No recovery	No recovery	Partial recovery
Fetal outcome	Live	Live	Live	Live

eGFR- estimated glomerular filtration rate; DD- dialysis dependence; ESRD- end- stage renal disease.

The incidence of RCN is as high as in 10-30% of obstetric cases developing acute kidney injury while, only 5% of the non-gravid patients with acute renal insult develop RCN[17].The initial clinical picture in most cases of renal cortical necrosis is characterized by hypotension, severe enough to cause renal hypoperfusion to the extent of impairing renal autoregulatory defence mechanisms acts as an inciting event. This initiates a cascade of events damaging the local endothelium, and local activation of potent vasoconstrictors and coagulation factors. In the experimental work conducted by Apitz on pregnant rabbits highlighted the occurrence of Shwartzman reaction in response to single injection of endotoxin on the extremely vulnerable gravid endothelium[18].Postpartum haemorrhage complicating a good number of pregnancies, leads to severe hypovolemia due to massive haemorrhage, concomitant use of fibrinogen concentrates, occurrence of DIC, and the pregnancy related hypercoagulable state all leading to local endothelial damage, causing endovascular thrombosis and precipitating renal ischemia. Puerperal sepsis incites endotoxin mediated endothelial damage, causing vascular thrombosis compromising renal perfusion, facilitating cortical necrosis[7].

The gold standard for diagnosis of RCN is the histopathological examination of kidney biopsy tissue[7].A close differential diagnosis is acute tubular necrosis, which may also occur in a similar setting of acute kidney injury, albeit having a better prognosis than the former. It is also instrumental in picking up additional histopathological lesion such as TMA, which may have overlapping clinical and laboratory features in cases of sepsis and DIC. As TMA warrants specific treatment modalities like plasmapheresis, early diagnosis and treatment helps in early recovery of renal function. This was seen in one of the patients in our case series.

Renal biopsy, being an invasive diagnostic modality, warrants optimal coagulation parameters and hemodynamic stability of the patient. It also involves a considerable risk of post procedural complications such as bleeding, hematoma or arteriovenous fistula. In patients not medically fit to undergo renal biopsy or not consenting for the procedure, CT scan proves an excellent alternative non- invasive diagnostic method for an early diagnosis. As radio-iodinated contrast agents act as an additional nephrotoxic insult to the recovering kidneys, non-contrast CT scan also helps identifying cortical calcifications, seen in few of the cases for the presumptive diagnosis of RCN. Contrast enhanced CT and newer modalities like contrast enhanced USG (CES) scan with a good spatial resolution help diagnose of RCN from renal infarction showing non enhanced area with preserved hilar vascularity[19].

Literature shows a mortality rate as high as 86% in obstetrical RCN among studies done a few decades ago[20].Recently this incidence has shown a downward trend. An Indian study showed the maternal mortality rates of 11.7% and morbidity in the form of dialysis dependency to be 61.5% secondary to RCN[21].In our study, though there was no mortality, the development of ESRD was 50% as a consequence of RCN, showing significant morbidity and a grim prognosis. These two patients remained dialysis dependent even at 3 months follow-up. The prognosis of obstetric RCN patients developing end stage renal disease even after transplantation has not shown much of a hope, owing to the high incidence of hyperacute as well as acute rejections in the renal allograft, leading to early graft dysfunction in majority of the cases[22]. The graft survival rates post transplantation are consistently poor irrespective of the aetiology precipitating renal cortical necrosis.

Dialysis dependency in young women as a result of RCN places a considerable financial burden on the society, in turn affecting the social, mental and emotional well-being of the mother. The health and wellbeing of a mother reflect on the health and wellbeing of her family, and in turn on the society as a whole. Thus, ensuring all round care during pregnancy helps alleviate pregnancy related complications for improved maternal and fetal outcomes.

Conclusions

The incidence of RCN in cases of pregnancy related AKI is like the tip of an iceberg and warrants attention. Strategies need to be formulated and implemented for the alleviation and reduction of preventable causes of RCN in pregnancy. Better medical care facilities, regular ante natal check-ups and regular monitoring for early detection and management of pregnancy related complications, training of personnel reducing the incidence of septic abortions and puerperal sepsis and emphasis on institutional deliveries need to be ensured. Prevention is better than cure. These changes will help improve maternal and fetal outcomes.

Limitations

Our study was a retrospective study, with a smaller sample size of 4 patients. Also, the short period of follow -up of 3 months post-partum are the limitations of our study.

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