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A Prospective Analysis of Feto - Maternal Outcomes in Pregnancy Related Acute Kidney Injury

Kanmani[1], Muruga Lakshmi [2], Kavya[3]

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Coimbatore Medical College, India

[2]Professor, Department of Obstetrics and Gynaecology, Coimbatore Medical College, India

[3]Junior Resident, Department of Obstetrics and Gynaecology, Coimbatore Medical College, India

Abstract: ***Background: The incidence of pregnancy related acute kidney injury in pregnancy (PRAKI) has declined significantly over the last three decades in developing countries. However, it is still associated with significant feto - maternal morbidity and mortality. The risk factors associated with advanced maternal age such as hypertension, diabetes, chronic kidney disease, and those associated with reproductive technologies such as multiple gestations are increasing. Traditional causes of PRAKI, such as septic abortions and puerperal sepsis, have been replaced by hypertensive diseases, such as preeclampsia and thromboticmicroangiopathies comprising thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS). Aim: Our study aimed at analyzing the etiological factors, clinical presentation and feto - maternal outcomes of patients with pregnancy related acute kidney injury. Material and Methods: A prospective observational study of patients with obstetric complication and pregnancy related medical conditions leading to acute kidney injury was conducted for a period of one year. Factors' contributing to acute kidney injury during pregnancy and puerperium and their feto maternal outcome was studied. Results: Out of 12953 obstetric admissions and 9099 deliveries in one year, the incidence of PRAKI was 3.3%. Severe preeclampsia was the major contributing factor for PRAKI with 38%. 58% of the patients were multigravida.72%developed AKI in third trimester and puerperium. HUS and sepsis were associated with higher mortality. Incidence of mortality is 33% among pregnancy complicated with AKI. This accounted to about 18% of total maternal deaths in our institution.66 % of patients recovered with no prolonged morbidity.9% of the pregnancies with AKI progressed to ESRD. Our study reported 29% perinatal mortality in the pregnancies with AKI. The implementation of specific interventions for the prevention, diagnosis and management of AKI in pregnant women may reduce the maternal and fetal morbidity and mortality.***

Keywords: PRAKI, ESRD, HUS

1. Introduction

AKI is a heterogeneous syndrome in pregnant women and can be caused by multiple factors. It occurs typically in otherwise healthy women who develop obstetrical complication or acquired pregnancy - related medical condition. Usually, the development of PRAKI follows a bimodal distribution with two incidence peaksone in the first trimester caused by septic abortion and other in the third trimester and/or around the time of delivery due to late obstetrical complications. However, several etiologies not related to pregnancy like acute gastroenteritis, malaria, pyelonephritis, lupus nephritis, and acute interstitial nephritis are also reported to cause AKI in pregnancy. The incidence of PRAKI in developing countries, accounts for 5%–20% of total AKI population. Approximately 75% cases of AKI occur during the late third trimester and in the early postpartum period. Approximately 1% of women with severe Preeclampsia and 3%–15% of women with HELLP syndrome develop AKI. Other causes include septic abortion, puerperal sepsis, antepartum hemorrhage (APH) or postpartum hemorrhage (PPH), intrauterine death, acute fatty liver of pregnancy (AFLP), and thrombotic microangiopathy of pregnancy.

Aim

Our study aimed at analyzing the etiological factors, clinical presentation and feto - maternal outcomes of pregnancy related acute kidney injury.

2. Review of Literature

Acute Kidney Injury in Pregnancy

Acute Dialysis Quality Initiative (ADQI) group convened an International Consensus Conference of experts in the field and agreed upon a definition of ARF. Furthermore, the group created the "RIFLE" classification system based on changes from the patient's baseline either in serum creatinine level or GFR, urine output, or both. The purpose of RIFLE, which is the acronym for Risk, Injury, Failure, Loss, and End - stage kidney disease (ESKD), is to classify patients at separate risk for development of ARF.

RIFLE CRITERIA to Determine Risk for ARF *Serum Creatinine/GFR Urine Ouput*
Risk Serum Cr increased 1.5× *or* GFR decreased more than 25% Less than 0.5 mL/kg/hr for 6 hr
Injury Serum Cr increased 2.0× *or* GFR decreased more than 50% Less than 0.5 mL/kg/hr for 12 hr
Failure (hours) Serum Cr increased 3.0× *or* GFR decreased more than 75% *or* Serum Cr greater than 4 mg/dL *or* Serum Cr acute rise greater than 0.5 mg/dL Less than 0.3 mL/kg/hr for 24 hr***or*** anuria for 12 hr
Loss Persistent AKI; complete loss of kidney function for more than 4 weeks
ESKD End stage kidney disease for longer than 3 months

Preeclampsia is associated with altered hemodynamic abnormalities such as decreased renal plasma flow, reduction in GFR by 30%–40%, and renal vasoconstriction. Thus, kidney in preeclamptic women is highly susceptible to ischemic injury. Renal tubular secretion of uric acid is impaired in preeclampsia, resulting in elevated concentration of uric acid in the blood. AKI occurs in approximately 1% of women with severe preeclampsia. AKI mostly occurs antepartum, but development of AKI in the early postpartum was reported. AKI most often develops in the setting of complication of preeclampsia such as placental abruption, disseminated intravascular coagulation (DIC), sepsis, postpartum bleeding, or intrauterine fetal death. Reversal of AKI occurs following delivery of fetus in majority of patients with preeclampsia, The most common histological lesion in the setting of AKI in patients with preeclampsia/HELLP syndrome is acute tubular necrosis (ATN).

AKI is reported in 3%–15% cases of HELLP syndrome, and overall, it may account for 40% of all cases of P - AKI and may increase up to 60% of cases in severe form of this disease. Dialysis is needed in approximately 10%–46% of patients with HELLP syndrome associated AKI during acute phase. However, even dialysis - requiring AKI has excellent prognosis with complete recovery of renal function in almost all cases. Thus, majority (93%–100%) of patients with HELLP syndrome - related AKI have near complete reversal of renal function. The progression to CKD is reported to occur in < 10% of patients who developed AKI on preexisting renal disease and/or hypertension. Thus, prognosis of AKI in patients with HELLP syndrome is favourable.

AKI in patients with AFLP is mostly mild and without need for dialysis support. In most women, there is complete liver and kidney recovery after delivery. Renal insufficiency in AFLP is usually nonoliguric although oliguria and ATN can occur in the setting of hemorrhage - induced hypovolemia. The various factors that may contribute for AKI in AFLP include hypovolemia, coexisting PE, coagulopathy, hepatic failure, and intra - abdominal hemorrhage. The urgent and immediate delivery of fetus is associated with favorable maternal and fetal prognosis.

P - TMA associated with complement activation pathway (CAP) dysregulation clinically presents as atypical HUS (aHUS). Clinical features of aHUS are similar to TTP, but renal involvement is more severe (serum creatinine >2.3 mg/dl) and the neurological manifestation is rare. aHUS occurs mainly in the first 6 months postpartum. Pregnancy and delivery are usually uneventful in majority of the patients. The CLASSICAL pentid of HUS are microangiopathic haemolyticanaemia, thrombocytopenia, fever, renal impairment and CNS abnormalities. All the clinical presentation overlap with that often more common HELLP SYNDROME, an accurate diagnosis is essential as the management of two syndromes differ.

The clinical and hematological features of HUS/TTP and PE/HELLP are similar because both have MAHA, thrombocytopenia, and renal disease. Further, concomitant PE/HELLP syndrome may occur in approximately 20% of women with pregnancy - associated TMA severe PE/HELLP is generally an indication for expedient delivery, while TTP typically responds to plasma exchange, with continuation of the pregnancy for weeks to months. Further, concomitant TTP and PE/HELLP syndrome carry very high (44.4%) maternal mortality. Therefore, both delivery and plasma exchange are probably indicated to optimize chances for maternal survival. The clinical clues for the diagnosis of pregnancy - associated TTP/HUS are as follows:

1) The coagulation abnormalities such as elevated antithrombin, elevated D - dimer, and high fibrinogen levels are absent in TTP/HUS while they are common in HELLP syndrome
2) Isolated LDH increase with normal hepatic transaminase favors HUS/TTP
3) Severely increased hepatic transaminases level strongly suggests HELLP syndrome.

3. Materials and Methods

This prospective observational study was conducted on patients diagnosed with pregnancy related acute kidney injury in the Department of Obstetrics and Gynecologyat tertiary care teaching hospital from January 2020 to December 2020. The study was approved by the institutional human ethics committee. Patients who satisfied the inclusion and exclusion recruited in the study after obtaining informed written consent. The inclusion criteria used in the study was previously healthy pregnant women who developed acute kidney injury during pregnancy or puerperium. Acute kidney injury (AKI) was defined as a) elevation of serum creatinine from baseline by 1.5 times, or2) oliguria - urine output less than 0.5 mL/kg/hr for more than 6hours as per RISK category of RIFLES criteria. Pregnant women who had either 1) renal disease prior to pregnancy 2) Renal scarring or small size of the kidneys in ultrasonography, or 3) elevated serum creatinine prior to gestation were excluded from the study.

All the investigations and management decision including the mode of delivery were carried out as per treating surgeon’s discretion. General physician and nephrologist opinion was obtained and treated as appropriate. Data on demographics, clinical features, laboratory results, treatment details and feto - maternal outcomes were collected and entered in Microsoft excel spreadsheet

Statistical analysis was performed using SPSS/Microsoft.

4. Results

From January 2020 to December 2021, our department had 12953 obstetric admissions and 9099 deliveries. Among them 21 patients developed PRAKI and were included in the study. The incidence of PRAKI in our study was 3.3%. The baseline demographic and clinical characteristics of the study population are mentioned in table 1 and 2. Almost all the patients had a precipitating factor which led to AKI. Severe preeclampsia was the most common precipitating factor. Preeclampsia, postpartum haemorrhage, HELLP, HUS, sepsis were associated with AKI in decreasing order of incidence. Out of 179 severe preeclampsia in our

institution 10 were having AKI which constitutes to around 5.5%. Out of 35 Abruption, 3 went for AKI which is around 8%. Patients presented with decreased urine output with elevated creatinine values. Associated symptoms and signs were fever, anemia, thrombocytopenia, jaundice, fever, proteinuria, DIC and neurological deficits. Lab results of the patients are represented in figure 1. Haemoglobin and platelets were as low as 4.6 gms /dl and 23000 thousand/mm3 in our patients. Serum creatinine was as high as 7.4 in our study population.48% of the patients who had AKI were delivered by caesarean section.58% of the patients were multigravida.62% of the patients had delivered live babies, out of which 4% were FGR and 2% were delivered preterm.6% has stillbirth.72%developed AKI in third trimester and puerperium. .66 % of patients recovered with no prolonged morbidity.33 % recovered by conservative management. About 47% had transfusion of blood and blood products.23 % were given steroids.67% were on dialysis. HUS and sepsis were associated with higher mortality. Incidence of mortality is 33% among pregnancy complicated with AKI. This accounted to about 18% of total maternal deaths in our institution. Patients in risk were having complete recovery. PRAKI with injury showed 75% recovery. Failure and loss showed 71% and 50% recovery. ESRD patients with PRAKI showed 100% mortality.

Table 1: Baseline Demographic Characteristics

Population characteristics	Values
Age in years, mean (SD)	26 (median)
Age distribution, n (%)	
Less than 20 years	7 (33)
20 to 30 years	11 (52)
More than 30 years	3 (15)
Parity, n (%)	
Primigravida	9 (42)
Multigravida	12 (58)
Outcome of pregnancy, n (%)	
Vaginal delivery	8 (39)
Caesarean section	10 (48)
Abortion	3 (9)
Timing of PRAKI diagnosis, n (%)	
First trimester	2 (9)
Second trimester	4 (19)
Third trimester	9 (43)
Puerperium	6 (29)

Table 2: Clinical Characteristics, Management and Outcome

Clinical presentation, n (%)	
Hypertension	18 (85)
Fever	4 (19)
Jaundice	10 (47)
Anemia	11 (52)
Thrombocytopenia	18 (85)
Oliguria	13 (61)
Proteinuria	4 (19)
Edema	8 (38)
Disseminated intravascular coagulation	2 (9)
Causes leading to PRAKI, n (%)	
Preeclampsia/HELLP	10 (38)
TTP HUS	3 (14)
Portal hypertension	1 (4)
Antepartum haemorrhage	3 (14)
Postpartum haemorrhage	4 (20)
Sepsis	2 (10)
RIFLE Criteria, n (%)	
Risk	4 (19)
Injury	4 (19)
Failure	7 (34)
Loss	4 (19)
End stage renal disease	2 (9)
Management, n (%)	
Conservative	7 (33)
Blood product transfusion	10 (47)
Steroids	5 (23)
Hemodialysis	14 (67)
Maternal outcome, n (%)	
Mortality	7 (34)
Recovered	14 (66)
Causes of maternal mortality, n (%)	
Sepsis	2 (28)
Hemorrhagic shock	1 (15)
TTP HUS	3 (42)
Portal hypertension	1 (15)
Fetal outcome, n (%)	
Abortion	2 (9.5)
Still birth	6 (28.5)
Live birth	13 (62)
Neonatal morbidity, n (%) N=13	
Fetal growth restriction	4 (30.8)
Prematurity	2 (15.4)

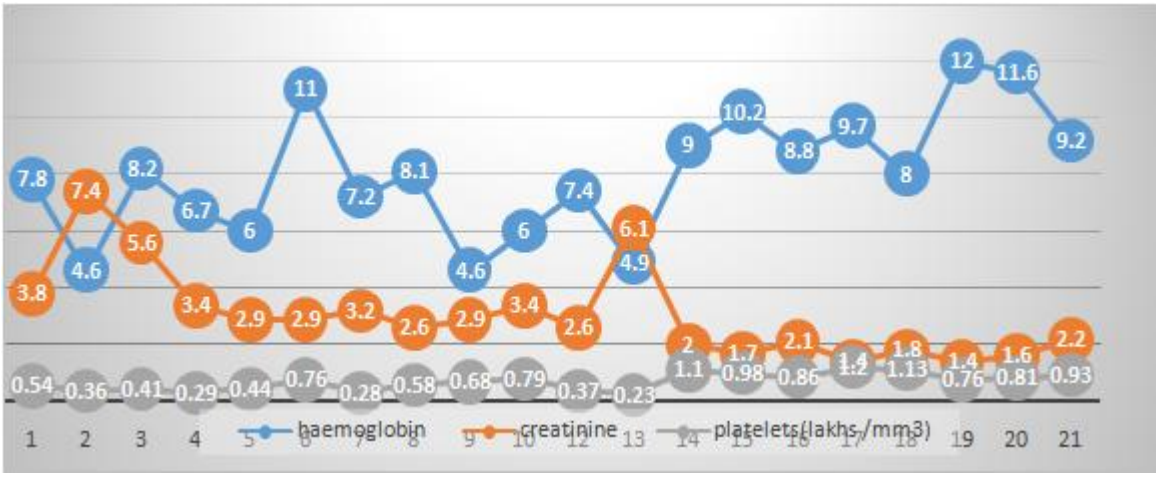

Figure 1: Trends in Laboratory Values

5. Discussion

AKI in pregnancy is a serious complication which can have a significant impact on the mother and fetus. We described 21 patients with PRAKI during the study period. The incidence of PRAKI in our institute during the study period was 3.3%.21 out of 631 AKI patients were having pregnancy associated AKI. In a study done by J Prakash et al in 2017 at Uttar Pradesh the incidence was around 5 – 20 %, whereas in a Canadian study done in 2018 Swathi Rao et al the incidence was 1.6% - 2.8%. Lower incidence in developed countries is due to legalization of abortion and improvement in obstetric and antenatal care. in an Indian study in Karnataka by Mahesh et al in 2017, the incidence of PRAKI was 3 - 7%.

The mean age of patients studied was 26. The median age was 27 years in women without pregnancy - related AKI hospitalization versus 28 years in women with pregnancy - related AKI hospitalizations in a study by lieu et al in China 2017. E Mahesh et al study in Karnataka 2017 showed the median age of occurrence of PRAKI as 25.

Patients presented with decreased urine output with elevated creatinine values. Associated symptoms and signs were fever, anemia, thrombocytopenia, jaundice, fever, proteinuria, DIC and neurological deficits. Almost all the patients were hypertensive. Nearly 85% of the patients had associated anemia with thrombocytopenia.9% 0f the patients went in for DIC.4% of the patients had fever during the course of the disease.

Almost all the patients included in our study had a precipitating factor which led to AKI. Severe preeclampsia was the most common precipitating factor. Preeclampsia with HELLP and postpartum hemorrhage accounted for 38% and 20 % of AKI in our study. HUS and APH were the cause for 14 % AKI each. Sepsis was the precipitating factor for 10% of the patients included in our study. In a study in Uttar Pradesh by Prakash J and ganiger in 2017 showed the incidence of septic abortion associated AKI as 5%. The same study showed preeclampsia associated AKI to as 43%. In a study by E Mahesh et al in Karnataka 2017, sepsis and preeclampsia as the leading causes for AKI with 4 % and 56% respectively. Out of 179 severe preeclampsia in our institution, 10 was having AKI which constitutes to around 5.5%. Out of 35 Abruption, 3 went for AKI which is around 8%. That is the incidence of AKI in preeclampsia and abruption is 5.5% and 8% respectively.

48% of the patients who had AKI were delivered by caesarean section.39% were delivered vaginally.13% were aborted.58% of the patients were multigravida.10 out of 21 pregnancies with AKI went for caesarean (48%), whereas 4381 out of 9078 went for caesarean in pregnancies without AKI (48%). In a research article, seven studies reported 247 cesarean deliveries in 337 women with PR - AKI and 1574 cesarean deliveries of the 4013 women without AKI, producing a 1.49 - fold AKI during pregnancy was associated with a higher risk. In our study there was no increased caesarean in pregnancies with AKI. Most of the patients developed AKI in third trimester and puerperium with 43% and 29% respectively. In the study in 2017 by j Prakash et al in UP, India 75% of AKI complicated pregnancy in the third trimester and early puerperium Mahesh et al in 2017 study in Karnataka, had 60% of PRAKI patients in puerperium and 32% in the third trimester.

14 out of 21 AKI associated pregnancy (66%) were requiring dialysis during the disease course. The incidence of pregnancy AKI requiring dialysis was 15 per 10000 deliveries in our study. The incidence in PR - AKI requiring dialysis was 0.36 per 10, 000 deliveries and maternal mortality associated with PRAKI 0.23 per 10, 000 deliveries in the United States in a study done by Silvi shah and Karthikeyan Meganathan et al in - KIDNEY CARE, university in USA in 2019. In Canada, in 2018 a study by Swati Rao et al the incidenceof severe PR - AKI requiring dialysis was as low as <1in 10, 000 pregnancies. In Africa, a recent study in 2018 from Morocco reported 6.6 cases of PR - AKI per 1000 deliveries, with 16% requiring dialysis.8.8% of pregnancy with AKI required dialysis in a study in 2020 by Silvi Shah and Karthikeyanmeganathan in KIDNEY CARE programs, a university in USA.

As per RIFLES criteria, in a study by E Mahesh in Karnataka 2017 22% were in risk, 36% were in injury, 34 % in failure, 5% in loss and 2% in ESRD. In our study 19% were in risk, injury, loss category and 34% in failure.9% of the pregnancies with AKI progressed to ESRD in our study. In our study, Patients in risk were having complete recovery. PRAKI with injury showed 75% recovery. Failure and loss showed 71% and 50% recovery. ESRD patients with PRAKI showed 100% mortality.2.5% women with AKI during pregnancy progressed to ESRD and needed long - term dialysis in a study by swati et al in USA.28 % required dialysis for more than 6 weeks in our study. Less severe PR - AKI demonstrates favorable renal recovery at 40% to 75%, but 4% to 9% of women with severe PR - AKI remained dialysis dependent at 4 to 6 months postpartum in a study by Swati et al in Canada 2018.

Incidence of maternal mortality was 33% in women with pregnancies complicated with AKI in our study. This accounted to 18 % of total maternal deaths. HUS and sepsis associated AKI in pregnancy were associated with higher mortality of 42 % and 28 %. In the study done by lieu et al in China, in 427 women with PR - AKI there were 57 deaths which was about 13.3%. In our study 7 deaths occurred among 21 women with pregnancy AKI which was about 33%. Pregnancies with AKI contributed to 18% of total maternal deaths in our study. Recent studies from China and India report maternal mortality rate associated with PR - AKI of 4.0% and 5.8%, respectively.

6 out of 21 pregnancies (29%) with AKI went for stillbirth in our study. Lieu et al in China 2017 reported 123 stillbirth/perinatal deaths of the 412 pregnancies with PR - AKI which accounted to 29.8%. Studies from India in 2018 published in Kidney internal reports have reported high perinatal mortality of 20% to 45% due to intrauterine death, stillbirth, and prematurity. In China, perinatal mortality was 17%. Our study reported 29% perinatal mortality in the pregnancies with AKI.

6. Conclusion

The management of AKI during pregnancy is a major clinical challenge because it poses a risk to both mother and fetus. Pregnancy - related AKI is associated with an increased risk of mortality, higher health care utilization, and longer length of hospital stays. The present study increases the awareness of pregnancy - related AKI and suggests improvement to AKI - related care. The implementation of specific interventions for the prevention, diagnosis and management of AKI in pregnant women may reduce the burden of AKI during hospitalizations. Identification of underlying etiology of PR - AKI is not always straightforward and very much depends on timing, risk factors, and sometimes a therapeutic trial (i. e., steroids for lupus nephritis). More research is sorely needed to develop preventive and treatment modalities, as especially pregnancies in women with preexistingcomorbidities and risk factors for PR - AKI are increasing.

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