Pregnancy Related Acute Kidney Injury: A Single Tertiary Care Center Experience

Original Article

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ABSTRACT

Objective: To describe an Egyptian single tertiary care center experience regarding the incidence, etiology and maternal and perinatal outcomes of pregnancy-related acute kidney injury (PR-AKI).

Materials and Methods: This was a retrospective analysis of prospectively collected data of women with AKI admitted to Mansoura University Hospital (MUH) during pregnancy or two weeks postpartum for a pregnancy- or delivery-related cause. All patients were followed up for 3 months from the time of AKI diagnosis in order to assess the maternal outcome (recovery, non-recovery or mortality). Patients who did not require dialysis were compared with those who required dialysis.

Results: Over the 1.5-year study period, 18 patients with PR-AKI were admitted to MUH, representing a cumulative incidence of 4.1 per 1000 deliveries. Out of these patients, 10 patients (55.6%) required dialysis while the other 8 patients (44.4%) did not require dialysis. The commonest cause of AKI was severe preeclampsia (50%) and other causes included AFLP (16.7%), hemorrhage (16.7%) and sepsis (16.7%). Thirteen cases (72.2%) had complete recovery of kidney function while 2 cases (11.1%) did not have complete recovery after the 3-months follow up period. Maternal mortality occurred in 3 cases (16.7%) who had sepsis and hemorrhage.

Conclusion: Preeclampsia, represent the commonest cause of PR-AKI, and although it has a favorable maternal outcome, the perinatal outcome is very poor. Obstetric hemorrhage had not become the leading cause of PR-AKI, but delayed referral of cases with severe peripartum bleeding, especially when associated with sepsis, is responsible for most of the maternal mortalities.

Key Words: Acute kidney injury, maternal mortality, obstetric hemorrhage, preeclampsia, sepsis.

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INTRODUCTION

Acute Kidney Injury (AKI) is considered a clinical syndrome which mainly manifests itself as a rapid deterioration of the kidney function and is linked to high rates of morbidity and mortality[1]. Despite much improvement in health care, this remained unsolved major public health care problem all over the world as more than 13 million people have AKI each year, the majority of them (about 85%) are resident in developing countries with low resources[2]. The AKI was considered in the past a reversible disease, but more extensive research had revealed that it may affect the future health and is linked to ongoing hypertension, cardiovascular diseases and even in some cases it may lead to permanent affection of kidney function known as chronic kidney disease (CKD) with its related mortality[2-5].

Pregnancy-related AKI (PR-AKI) is considered one of the most important obstetric complications as it is a common cause for intensive care unit (ICU) admission, termination of pregnancy (TOP), commonly before fetal maturity, and need for dialysis during the peripartum period. It has a high association with both maternal and perinatal morbidity and mortality. Maternal mortality had ranged from 9% to as high as 55%[6, 7].

The incidence of PR-AKI varies greatly between developed and developing countries. In India, there was a marked decrease in the proportion of PR-AKI among patients with AKI as this figure was 15% in 1980s and declined ten folds to 1.5% in 2010s. Despite this, PR-AKI remained a serious problem as about one third of these recent cases required dialysis[7, 8]. In China, the incidence of PR-AKI had also declined to range of 0.2-1.8% with about 6% of cases requiring dialysis[9]. The legalization of TOP in developed countries had attributed to decrease the incidence of PR-AKI[10-12]. However, in Canada, it was observed that the incidence started to rise again recently from 1.6 per 10000 deliveries in 2003 to 2.3 per 10000 deliveries in 2008. Similar rise was also noted in USA, from 2.3 per 10000 in 1998 to 4.5 per 10000 in 2008[13].

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Obstetric causes that lead to AKI include those related to the first trimester mainly septic abortion and hyperemesis gravidarum, and those related to third trimester as hypertensive disorders (which are considered to be the most common causes especially in developed countries), obstetric hemorrhage, acute fatty liver of pregnancy (AFLP), hemolytic uremic syndrome and sepsis during postpartum period[13-15].

The diagnosis of AKI during pregnancy may be challenging as the hemodynamic and vascular changes that occur in normal pregnancy are associated with about 50% increase in the glomerular filtration rate (GFR) which mean that the serum creatinine that is considered normal in non-pregnant ladies may represent variable degrees of renal function compromise during pregnancy. The definition and classification of AKI in general population is dependent on the AKIN (Acute Kidney Injury Network) and RIFLE (Risk, Injury, Failure, Loss, and End Stage) criteria, but they cannot be validated during pregnancy[16].

The management of PR-AKI needs a multidisciplinary team that includes obstetricians, nephrologists, and ICU personnel. This includes supportive measures and may require renal replacement therapy in some cases. One of the most important points in the management is the treatment of underlying obstetric cause. The outcome is variable and includes complete recovery of kidney function (in about 40-75% of cases), partial recovery of kidney function (4-9% require dialysis at 4-6 months after delivery), and progression to end stage renal disease (1.5-2.5% of cases)[15-18].

The high rates of pregnancies and deliveries in our locality together with lack of proper prenatal care, especially in rural areas, had made AKI in pregnancy a major problem affecting young women in their child bearing period making mortality rates unaccepted in modern obstetrics and taking into consideration the long term morbidity in a proportion of the survivors. From this point, we aimed in our study to highlight the prevalence of PR-AKI in our tertiary care center, the most common causes and outcome in order to implement strategies that may help in decreasing the incidence of this problem through prevention and early prober intervention of some pregnancy related complications.

PATIENTS AND METHODS

Study design:

This was a retrospective analysis of prospectively collected data of women with PR-AKI who were admitted to Mansoura University Hospital (MUH), Egypt during the period from March 2022 through August 2023. The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. R.23.10.2351). The main inclusion criterion was women with AKI admitted to MUH during pregnancy or two weeks postpartum for a pregnancy- or delivery-related cause. Women with any of the following criteria were excluded from the study: 1) preexisting kidney disease or renal insufficiency before pregnancy; and 2) AKI due to none obstetric cause. The AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes (KIDGO) creatinine and urine output criteria[19] by presence of any of the following parameters: 1) increase in serum creatinine ≥ 0.3 mg/dl within 48 hours; 2) increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or 3) urine volume of < 0.5 ml/kg/h for 6 hours.

Collection of the patient's data:

A database derived from the patient's hospital and perinatal records was used. The following clinical characteristics were evaluated: maternal age, previous gestations, parity, mode of conception, preexisting medical condition, gestational age at TOP, the cause of AKI, timing of occurrence of AKI with respect to TOP (before or after TOP), peak serum creatinine level and the need for dialysis. The baseline data was evaluated according to the lowest value available closest to the admission date within the previous 3 months. Data for women receiving regular prenatal follow up were obtained from their follow up records while data for women without prenatal follow up were obtained from occasional measurements at any medical service center.

Related diagnostic criteria:

The diagnosis, classification and severity of hypertensive disorders during pregnancy, including gestational hypertension, preeclampsia/eclampsia, chronic hypertension and chronic hypertension with superimposed preeclampsia, were determined according to the American College of Obstetricians and Gynecologists (ACOG) criteria[20, 21]. The hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome was diagnosed according to the following criteria[22]: 1) lactate dehydrogenase (LDH) ≥ 600 IU/L; 2) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated more than twice the upper limit of normal; and 3) platelets count < 100000 per microliter of blood.

The diagnosis of acute fatty liver of pregnancy (AFLP) was determined according to the Swansea criteria[23], including: 1) vomiting; 2) abdominal pain; 3) polydipsia/polyuria; 4) encephalopathy; 5) leukocytosis (leukocytic count > 11000 cells per microliter of blood); 6) coagulopathy (prothrombin time > 14 sec or activated partial thromboplastin time > 34 sec); 7) hypoglycemia (blood glucose < 72 mg/dl); 8) elevated liver enzymes (AST or ALT > 42 IU/l); 9) bilirubin > 0.8 mg/dl; 10) creatinine > 1.7 mg/dl; 11) ammonia > 27.5 mg/dl; 12) uric acid > 5.7 mg/dl; 13) ascites or bright liver on ultrasound scan;

and 14) microvesicular steatosis on liver biopsy. Presence of at least 6 out of the 14 Swansea criteria, in absence of another explanation, confirms the diagnosis AFLP.

Follow up of the patients and determination of their outcomes:

Intermittent hemodialysis was prescribed using the standard indications of dialysis in

patients with dialysis requiring AKI[24]. All patients were followed up for 3 months from the time of AKI diagnosis in order to assess the outcome. The maternal outcome was categorized as: 1) recovery, with returning of serum creatinine and urine output to normal levels; 2) non-recovery, with persistent rise in serum creatinine (>1.4 mg/dl) and/or dependence on dialysis; or 3) mortality. The perinatal outcome was categorized as 1) live birth; 2) fetal loss, including miscarriage and intrauterine fetal death (IUFD); and 3) early neonatal death (END), defined as death occurring at up to 28 days of life. The midtrimester abortion (MTA) was defined as TOP between 13 and 26 weeks of gestation as calculated from the last menstrual period[25].

Statistical analysis:

Using SPSS 22.0, the data were analyzed. Data for quantitative variables were expressed as mean ± SD or median (min-max) as appropriate. Categorical variables were described as counts and percentage. Continuous variables were analyzed with the Student t test or the Mann Whitney U test as appropriate. The categorical variables were tested using the Chi-squared or Fisher's exact tests as appropriate. The statistical significance was determined using a $P \leq 0.05$ criterion.

RESULTS

Over the 1.5-year study period, there were 4390 deliveries in MUH, and there were 18 patients with PR-AKI admitted to MUH, representing a cumulative incidence of 4.1 per 1000 deliveries. Out of the 18 patients with PR-AKI, 10 patients (55.6%) required dialysis while the other 8 patients (44.4%) did not require dialysis.

Table 1 displays the demographic and obstetric characteristics of the total study cohort and among the subgroups according to need for dialysis. Fourteen patients (77.8%) did not have any preexisting medical condition while one patient (5.6%) had chronic hypertension, 2 patients (11.1%) had bronchial asthma and one patient (5.6%) had hypothyroidism. Sixteen patients (88.9%) conceived spontaneously while 2 patients (11.1%) conceived by intracytoplasmic sperm injection (ICSI) and these 2 patients had multifetal pregnancy. The mean gestational age at TOP was 30.27 ± 5.91 weeks. In 2 patients, pregnancy had been terminated before 26 weeks (MTA) and in 16 patients, TOP was after 26 weeks of gestation (one patient had vaginal delivery and 15 patients underwent CS). No significant difference between the patients who did not require dialysis and those who required dialysis in the demographic and obstetric characteristics.

Table 2 shows the clinical characteristics of the total study cohort and among the subgroups according to need for dialysis. The commonest cause of AKI was severe preeclampsia (50%) and other causes included AFLP (16.7%), hemorrhage (16.7%) and sepsis (16.7%). Out of the 9 cases of severe preeclampsia, HELLP syndrome occurred in 7 cases. The mean peak serum creatinine was 6.90 ± 4.54 mg/dl and it was significantly higher in patients who required dialysis than in those who did not require (8.81 ± 4.45 vs 4.51 ± 3.60 mg/dl; $P = 0.007$). The median duration to reach peak serum creatinine was 7 days (range = 1-24 days) and this duration was significantly longer in patients who required dialysis than in those who did not require (2 vs 13 days; $P = 0.003$). The median hospital stay period was 19 days (range = 1-66 days) and this period was significantly longer in patients who required dialysis than in those who did not require (11.5 vs 31.5 days; $P = 0.007$).

Table 3 displays the maternal and perinatal outcomes among the total study cohort and among the subgroups according to need for dialysis. Thirteen cases (72.2%) had complete recovery of kidney function while 2 cases (11.1%) did not have complete recovery after the 3-months follow up period and maternal mortality occurred in 3 cases (16.7%) who had sepsis and hemorrhage. The first mortality case had sepsis after laparotomy for placenta previa with antepartum hemorrhage (APH) and rupture uterus. The second mortality case had postpartum hemorrhage (PPH) and retroperitoneal hematoma. The third mortality case had atypical presentation of placenta percreta with hemoperitoneum. In completely recovered patients, the mean serum creatinine at recovery was 1.21 ± 0.08 mg/dl and the median duration to recovery was 17 days (rang = 6-55 days) and this duration was significantly longer in patients who required dialysis than in those who did not require (7 vs 26.5 days; $P = 0.010$).

Table 1: Demographic and obstetric characteristics of the total study cohort and among the subgroups according to need for dialysis

	Total cohort (n=18)	Subgroups according to need for dialysis		
		Did not require dialysis (n=8)	Required dialysis (n=10)	*P value*
Age (years)*	28.53 ± 5.96	30.21 ± 5.90	27.18 ± 5.95	*0.374*
Gravidity †	3 (1-6)	3 (2-4)	1.5 (1-6)	*0.233*
Parity †	1.5 (0-4)	2 (0-2)	0.5 (0-4)	*0.779*
Prior VD †	0 (0-4)	0 (0-1)	0 (0-4)	*0.935*
Prior CS †	1 (0-3)	1.5 (0-2)	0 (0-3)	*0.396*
Preexisting medical condition‡				
No	14 (77.8%)	7 (87.5%)	7 (70.0%)	*0.281*
Hypertension	1 (5.6%)	1 (12.5%)	0 (0.0%)	
Bronchial asthma	2 (11.1%)	0 (0.0%)	2 (20.0%)	
Hypothyroidism	1 (5.6%)	0 (0.0%)	1 (10.0%)	
Mode of conception ‡				
Spontaneous	16 (88.9%)	7 (87.5%)	9 (90.0%)	*1.000*
ICSI	2 (11.1%)	1 (12.5%)	1 (10.0%)	
Multifetal pregnancy ‡	2 (11.1%)	1 (12.5%)	1 (10.0%)	*1.000*
Gestational age at TOP (weeks)*	30.27 ± 5.91	31.41 ± 2.50	29.36 ± 7.69	*0.594*
Mode of TOP ‡				
MTA	2 (11.1%)	0 (0.0%)	2 (20.0%)	*0.237*
VD	1 (5.6%)	0 (0.0%)	1 (10.0%)	
CS	15 (83.3%)	8 (100%)	7 (70.0%)	

* Expressed as mean ± SD and *P value* was calculated by the Mann-Whitney U-test.
† Expressed as median (minimum – maximum) and *P value* was calculated by the Mann-Whitney U-test.
‡ Expressed as frequency and percentage and P value was calculated by the Chi-Square test with Fischer's exact test as a correction for Chi-Square test when > 25% of cells have count < 5.
CS, cesarean section; ICSI, intracytoplasmic sperm injection; MTA, midtrimester abortion; TOP, termination of pregnancy; VD, vaginal delivery.

Table 2: Clinical characteristics of the total study cohort and among the subgroups according to need for dialysis

	Total cohort (n=18)	Subgroups according to need for dialysis		
		Did not require dialysis (n = 8)	Required dialysis (n = 10)	*P value*
Basal serum creatinine (mg/dl)*	0.78 ± 0.07	0.81 ± 0.08	0.75 ± 0.05	*0.092*
Cause of AKI †				
Severe preeclampsia	9 (50.0%)	5 (62.5%)	4 (40.0%)	*0.308*
AFLP	3 (16.7%)	2 (25.0%)	1 (10.0%)	
Hemorrhage	3 (16.7%)	1 (12.5%)	2 (20.0%)	
Sepsis	3 (16.7%)	0 (0.0%)	3 (30.0%)	
HELLP syndrome †	7 (38.9%)	3 (37.5%)	4 (40.0%)	*1.000*
Timing of AKI occurrence †				
Before TOP	8 (44.4%)	5 (62.5%)	3 (30.0%)	*0.342*
After TOP	10 (55.6%)	3 (37.5%)	7 (70.0%)	
Peak serum creatinine (mg/dl) *	6.90 ± 4.54	4.51 ± 3.60	8.81 ± 4.45	*0.007*
Duration to reach peak serum creatinine (days) ‡	7 (1-24)	2 (1-15)	13 (7-24)	*0.003*
Hospital stay (days)‡	19 (1-66)	11.5 (1-27)	31.5 (10-66)	*0.007*

* Expressed as mean ± SD and *P value* was calculated by the Mann-Whitney U-test.
† Expressed as frequency and percentage and *P value* was calculated by the Chi-Square test with Fischer's exact test as a correction for Chi-Square test when > 25% of cells have count < 5.
‡ Expressed as median (minimum – maximum) and *P value* was calculated by the Mann-Whitney U-test.
AKI, acute kidney injury; HELLP, hemolysis, elevated liver enzymes, and low platelet count; TOP, termination of pregnancy.

Table 3: Maternal and perinatal outcomes among the total study cohort and among the subgroups according to need for dialysis

	Total cohort (n=18)	Subgroups according to need for dialysis		
		Did not require dialysis (n = 8)	Required dialysis (n = 10)	*P value*
Maternal outcome *				
Recovery	13 (72.2%)	7 (87.5%)	6 (60.0%)	*0.330*
Non-recovery	2 (11.1%)	0 (0.0%)	2 (20.0%)	
Mortality	3 (16.7%)	1 (12.5%)	2 (20.0%)	
Serum creatinine at recovery (mg/dl) †	1.21 ± 0.08	1.17 ± 0.08	1.25 ± 0.05	*0.065*
Duration to recovery (days) ‡	17 (6-55)	7 (6-29)	26.5 (17-55)	*0.010*
Perinatal outcome *				
Live birth	5 (27.8%)	2 (25.0%)	3 (30.0%)	*0.956*
Fetal loss	9 (50.0%)	4 (50.0%)	5 (50.0%)	
END	4 (22.2%)	2 (25.0%)	2 (20.0%)	

* Expressed as frequency and percentage and *P value* was calculated by the Chi-Square test with Fischer's exact test as a correction for Chi-Square test when > 25% of cells have count < 5.
† Expressed as mean ± SD and *P value* was calculated by the Mann-Whitney U-test.
‡ Expressed as median (minimum – maximum) and *P value* was calculated by the Mann-Whitney U-test.
END, early neonatal death.

DISCUSSION

One of the fixed objectives at our obstetric tertiary care center is to improve the outcome with decreasing both maternal and perinatal morbidity and mortality. Although PR-AKI represents a direct consequence of pregnancy complications, many obstetricians have limited information about the disease spectrum because nephrologists and ICU personnel are more deeply involved in the management of this critical problem. Studying this disease from the obstetric point of view with emphasis on frequency of pregnancy complications associated with its development and the course of the disease became of utmost importance. We had represented 18 cases of PR-AKI admitted to our tertiary center. Most of these cases had TOP in third or late second trimester with the diagnosis of AKI made before TOP in 8 cases and after TOP in 10 cases.

Preeclampsia, including HELLP syndrome, was the most common cause of AKI in our study, representing about 50% of cases. Other less common causes were AFLP, obstetric hemorrhage, and pregnancy related sepsis, each is accounting for about 16.7% of cases. In preeclampsia, the reduced plasma volume together with the increase in vascular resistance of renal afferent arterioles result in reduction in renal perfusion and GFR, but levels that are below the non-pregnant state are rare and occur only with extreme degrees of the disease spectrum. Also, swollen endothelial cells of glomerular capillaries results in blocking of the filtration barrier which may result in increased serum creatinine to values seen in non-pregnant individuals[26].

Despite these changes, evident renal failure is rare in preeclampsia. Drakeley and his colleagues described 72 pregnant women with preeclampsia and AKI. About 50% of cases had HELLP syndrome and about one third of cases had placental abruption that augments the already present contracted blood volume in those patients[27]. In a previous study that was conducted at Mansoura Nephrology Center and included 40 patients with PR-AKI, preeclampsia and obstetric hemorrhage were the most common causes. This study included cases referred to nephrology center for dialysis, however, our study included cases with PR-AKI whatever dialysis was performed or not which means more precise assessment of the disease[28].

We had compared our results with a recent prospective study conducted in India, being one of the biggest countries containing centers with very high rates of referral for such cases. In this study, preeclampsia was also the most common cause of PR-AKI, accounting for 44.54% of cases, which is comparable to the 50% incidence that was reported in our study. Obstetric hemorrhage, sepsis and AFLP accounted for 35.4%, 28%, and 11% of cases; respectively[3]. In a meta-analysis and systematic review that included 31 studies between 1980 and 2021, the most common cause of PR-AKI was preeclampsia with other less common causes included septic abortion, APH, PPH, and AFLP[29].

Obstetric hemorrhage as a cause of PR-AKI accounted for only 16.7% in our cases and did not represent the leading cause of AKI in our study. In the developing countries, bleeding complications during pregnancy still represent a major cause of PR-AKI as evidenced from the Indian study where it accounts for 35.4% of all cases with PR-AKI[3]. One of the most important causes of obstetric hemorrhage in last decades is placenta accreta spectrum. There was a dramatic improvement in management of such cases at

our center because of multidisciplinary team management with proper prenatal diagnosis, increased surgical skills with incorporation of surgeons experienced in managing complex pelvic surgery, proper anesthetic management, and transfusion protocols of blood products. Also, other traditional causes of obstetric bleeding like atonic PPH and rupture uterus are better managed due to early referral, improved diagnosis, and early surgical intervention with no delay in decision of hysterectomy if indicated.

In our study, 10 cases (55.6%) needed dialysis while the rest of cases were managed without renal replacement therapy. This was higher than the Indian study in which only 26.4% of cases with PR-AKI needed dialysis[3] and comparable to the 55% rate that was reported in the meta-analysis including both hemodialysis and peritoneal dialysis[29]. The decision of dialysis was determined by nephrologist and ICU physician and followed the same indications in AKI that included presence of volume overload that is nonresponsive to diuretic therapy, presence of severe electrolyte and acid base abnormalities as persistent hyperkalemia refractory to medical treatment and presence of evident uremic manifestations as pericarditis or encephalopathy[24].

We had compared the group of patients that needed dialysis with those managed without and we found that there was no significant difference between the two groups regarding patient's demographic characteristics, mode of TOP and the cause of AKI. Peak serum creatinine level, duration to recovery and hospital stay period were significantly more increased in dialysis group. Complete recovery was higher, and mortality was lower in the non-dialysis group but did not reach a significant difference. Our study showed a high rate of complete recovery of patients with PR-AKI (72.2%). This was higher than the Indian study in which about 50% of cases showed complete recovery[3], and comparable to the 70.6% rate that was reported in the meta-analysis[29], and to the 62.5% rate reported in the Egyptian study[28].

The maternal mortality in our study was 16.7% (3 cases) which was comparable to the rates reported in other studies that varied between 12.7% and 22.5%[3, 28, 29]. When analysis was performed to the 3 cases with maternal mortality in our study, it was found that all cases shared presence of severe peripartum bleeding requiring massive transfusion, two of them had peripartum cesarean hysterectomy, and two had delayed referral at 7 or more days and arrived in severe compromised state and sepsis while the third was referred after irreversible hypovolemic shock.

Our study had showed poor perinatal outcome in patients with PR-AKI, with only 27.5% of patients having live birth, which was much lower than the 70% rate reported in the meta-analysis[29]. The poor perinatal outcome in our study could be explained by that preeclampsia, including HELLP syndrome, and AFLP represented about two thirds of our cases, and it is well known that these obstetric complications are associated with high rates of fetal demise, growth restriction, and severe prematurity when TOP becomes the main solution to save the mother's life.

The main strength point of our study lies in that, to the best of our knowledge, this is one of the limited studies that evaluated the disease of PR-AKI from the obstetric point of view. Another strength point is the inclusion of cases with PR-AKI who did not require dialysis and comparing them with those who required dialysis. The limitations of our study included the short period of the study, the small number of cases and the lake of long term (> 3 months) follow up of survivors.

CONCLUSION

We can conclude that preeclampsia, including HELLP syndrome, represent the most common cause of PR-AKI, and although it has a favorable maternal outcome, the perinatal outcome is very poor. Obstetric hemorrhage had not become the leading cause of PR-AKI, but delayed referral of cases with severe peripartum bleeding, especially when associated with sepsis, is responsible for most of the maternal mortalities.

CONFLICT OF INTEREST

There are no conflicts of interests.

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