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## Postpartum acute kidney injury: Single center observational study

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**Abstract---Background.** Postpartum acute kidney injury is a serious obstetric complication, and its diagnostic definition is highly variable in the literature. Recent studies reported an incidence up to 40% in both developed and developing countries. PP-AKI is associated with an increased risk of chronic kidney disease, and cardiovascular disease. **Methods.** We conducted a single center case control study for PP-AKI cases. Forty six women were recruited in the study, and they represented two groups, PP-AKI group (n=18), and healthy control group (n=38). Clinical examinations and laboratory investigations were collected. **Results.** Hypertension and CKD were reported in 5(27.8%), and 3(16.7%) of the included women in PP-AKI group respectively, while none of healthy control women had HTN, or CKD. PP-AKI patients exhibited significantly lower mean values for blood hemoglobin levels ( $7.9 \pm 1.36$  g/dl), platelets counts ( $157.9 \pm 92.3 \times 10^3/\text{mm}^3$ ), and serum albumin levels ( $2.9 \pm 0.4$  gm/dl) in comparison with healthy controls. Additionally, PP-AKI patients exhibited significantly higher mean value for serum creatinine levels

( $5.3 \pm 2.9$  mg/dl), and higher median and range values for prothrombin time 1(1-2.7) in comparison with healthy controls. Preeclampsia was the main possible etiology of PP-AKI. *Conclusion.* Postpartum AKI is a public health problem, which warrants implementation of preventive policies particularly in women with preexisting HTN and CKD.

**Keywords**---Postpartum, Hypertension, Preeclampsia.

## Introduction

Acute kidney injury that occurs during pregnancy or in the post-partum period is a serious obstetric complication with risk of significant associated maternal and fetal morbidity and mortality. Pregnancy related acute kidney injury (PR-AKI) was until recently believed to be a relatively rare and declining complication of pregnancy that was primarily associated with sepsis, complicated pregnancy terminations, and residence in low-income countries [1]. The lack of uniform diagnostic criteria limits the ability to accurately determine the incidence of PR-AKI and to quantify its influence on morbidity and mortality. Diagnostic definition of renal diseases related to pregnancy is not uniform and is highly variable in the literature--[2]. The American College of Obstetricians and Gynecologists (ACOG) defines renal insufficiency in the setting of hypertensive disorders of pregnancy as a serum creatinine level  $>1.1$  mg/dL or a doubling of the serum creatinine concentration in the absence of renal disease [3]. According to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, increase in SCr by  $26.5 \mu\text{mol/L}$  ( $0.3$  mg/dl) within 48 h or a 50% increase in SCr from the baseline within 7 days diagnose PR-AKI [4]. However, recent data suggests that the incidence of PR-AKI is increasing [5]. Melo et al. 2020, reported an incidence up to 40% in both developed and developing countries. According to different AKI definitions, PR-AKI incidence varied from 2.1% to 78.7% in developed countries and from 0.5% to 65% in developing countries [2]. PR-AKI is associated with an increased risk of chronic kidney disease (CKD), hypertension (HTN) and cardiovascular disease [6, 7]. Additionally, a recent study by Liu et al., reported that compared to non-pregnant women, pregnant women had a 51% increased risk of developing AKI that was independent of age and clinical comorbidities, suggesting that pregnancy increases the risk of AKI [8]. It occurs typically in otherwise healthy women who developed obstetrical complication or acquired pregnancy-related medical condition such as preeclampsia (PE) and/or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Approximately 75% cases of PP-AKI occur during the late third trimester and in the early postpartum. The hypertensive complications of pregnancy, particularly PE and/or HELLP, are the leading causes of PR-AKI in most parts of the world, including developing countries [9]. Approximately 1% of women with severe PE and 3%–15% of women with HELLP syndrome developed AKI. Other causes include postpartum hemorrhage (PPH), intrauterine fetal death, acute fatty liver of pregnancy (AFLP), and thrombotic microangiopathy of pregnancy (P-TMA). When all causes of AKI are considered, the frequency of dialysis of any duration is estimated to be 0–47% [10] but has been reported to be as high as 97% in developing countries such as India [11]. In comparison with pregnant women without AKI, those with Postpartum AKI (PP-AKI) may have underlying obstetrical hemorrhage, placental

abruption, disseminated intravascular coagulation and an increased mortality rate. Women with PP-AKI mostly have a longer stay in the ICU, a higher incidence of stillbirth/perinatal death, lower mean gestational age at delivery and lower birth weight [12]. There is a paucity of data on the incidence of PP-AKI and associated risk factors [13]. The present study aimed to assess the epidemiology of PP-AKI patients and their renal outcome.

## **Materials and methods**

We conducted a single center case control study for pregnant women who developed PP-AKI following delivery. AKI was defined as increase in SCr by  $26.5 \mu\text{mol/L}$  ( $0.3 \text{ mg/dl}$ ) within 48 h or a 50% increase in SCr from the baseline within 7 days according to KDIGO criteria [4]. All women aged 18 years and older, presented with AKI within the first three months after delivery, admitted to the nephrology or obstetric department in Mansoura university hospitals during 2020-2021 were recruited in the Postpartum AKI group. Women younger than 18 years, or older than 50 years old, and those who are unable to give informed consent, or have active malignancy, active infection, or active inflammatory processes were excluded from the study. Forty six pregnant women were recruited in the study, and they represented two groups, postpartum AKI group ( $n=18$ ), and healthy postpartum control group ( $n=38$ ). Clinical examinations, assessment of urine output (UOP), and routine laboratory investigations including urinalysis, protein/creatinine ratio, and serum creatinine were collected for our postpartum women. The study was approved by institutional research board of Mansoura faculty of medicine.

## **Statistical analysis**

The collected data were coded, processed, and analyzed using the statistical package for social science version 22 (SPSS) for windows. Categorized variables were presented as absolute numbers and percentage, while continuous variables will be expressed as mean  $\pm$  SD or median and range, depending on if the variable is normally distributed or not, as detected by the Kolmogorov–Smirnov Z test. For comparison among different groups, chi-square test was used for categorical data and either independent samples t-test or Mann–Whitney U test for continuous data with normal or skewed distribution, respectively. Spearman correlation analysis was used for nonparametric correlations. P value  $< 0.05$  was considered statistically significant.

## **Results**

Forty-six postpartum women were included in the current study. They are classified as healthy control group ( $n=38$ ), and postpartum AKI group ( $n=18$ ). No significant difference in age was detected between PP-AKI patients, and postpartum healthy controls ( $P = 0.784$ ). Hypertension and chronic kidney disease were reported in 5(27.8%), and 3(16.7%) of the included women in PP-AKI group respectively, while none of healthy control women had HTN, or CKD. A significantly higher mean systolic blood pressure was detected in PP-AKI group ( $124 \pm 26 \text{ mmHg}$ ). The most commonly used anti-HTN medication was CCBs followed by diuretics, BBs, and alpha methyl dopa for AKI cases.

Etiology based classification of PP-AKI patients included preeclampsia (n=5), Sepsis (n=3), postpartum hemorrhage (PPH, n=4), GN (n=1), thrombotic thrombocytopenic purpura (n=2), obstructive kidney diseases (n=2), and acute fatty liver of pregnancy (n=1), figure 1.

A highly significant statistical difference was detected in blood hemoglobin levels among the included groups ( $P \leq 0.001$ ), with significantly lower mean value in postpartum group ( $7.9 \pm 1.36$  g/dl). Additionally, a significant difference in platelets was demonstrated between the two included groups ( $P = 0.018$ ), with lower mean value for PP-AKI group ( $157.9 \pm 92.3 \times 10^3/\text{mm}^3$ ). Oppositely, non-significant difference was detected between the two groups as regard the total leucocytes count ( $P = 0.359$ ).

The PP-AKI patients exhibited high levels of proteinuria ( $2477 \pm 2532$ ) mg/day, with no significant statistical difference between the two groups ( $P = 0.106$ ). Mean serum albumin level was significantly lower in PP-AKI group ( $2.9 \pm 0.4$  gm/dl). There was a highly significant difference in serum creatinine levels among the included groups ( $P \leq 0.001$ ), and women with PP-AKI exhibited the higher values ( $5.3 \pm 2.9$ ) mg/dl. A significant statistical difference was reported in as regard prothrombin time among the included groups ( $P = 0.036$ ), with higher median and range values in PP-AKI group 1(1-2.7). Only three (23.1%) patients of PP-AKI group had negative urinary dipstick for proteinuria, table 1.

Table 1: sociodemographic, clinical, and laboratory characteristics of participant groups.

|                                    | Healthy pregnant control subjects (n = 38) | Postpartum AKI (n = 18) | P Value      |
|------------------------------------|--------------------------------------------|-------------------------|--------------|
| Age, years, mean $\pm$ SD          | 26.69 $\pm$ 5.84                           | 27.17 $\pm$ 6.3         | 0.784        |
| History of HTN, n (%)              | 0(0.0%)                                    | 5(27.8%)                | 0.001        |
| History of CKD, n (%)              | 0(0.0%)                                    | 3(16.7%)                | 0.010        |
| Systolic BP, mm Hg                 | 110 $\pm$ 13                               | 124 $\pm$ 26            | 0.027        |
| Diastolic BP, mm Hg                | 73 $\pm$ 9                                 | 79 $\pm$ 16             | 0.140        |
| Antihypertensive medication, n (%) |                                            |                         |              |
| Alpha methyl dopa                  | 0(0.0%)                                    | 7(38.9%)                | $\leq$ 0.001 |
| CCBs                               | 0(0.0%)                                    | 1(5.6%)                 |              |
| BBs                                | 0(0.0%)                                    | 13(72.2%)               |              |
| Diuretic                           | 0(0.0%)                                    | 3(16.7%)                |              |
| Diuretic                           | 223.7 $\pm$ 79.7                           | 157.9 $\pm$ 92.3        | 0.018        |
| WBC, ( $\times 10^3/\text{mm}^3$ ) | 200 $\pm$ 50                               | 2477 $\pm$ 2532         | 0.106        |
| HB, g/dl                           |                                            |                         |              |
| PLT, ( $\times 10^3/\text{mm}^3$ ) | 38(100.0%)                                 | 3(23.1%)                | $\leq$ 0.001 |
| 24hr.urinary protein, mg/day       | 0(0.0%)                                    | 2(15.4%)                |              |
| Dipstick proteinuria, n (%)        | 0(0.0%)                                    | 1(7.7%)                 |              |
| Negative                           | 0(0.0%)                                    | 5(38.5%)                |              |
| Trace                              | 0(0.0%)                                    | 1(7.7%)                 | $\leq$ 0.001 |
| 1+                                 | 0(0.0%)                                    | 1(7.7%)                 | $\leq$ 0.001 |
| 2+                                 | 0.6 $\pm$ 0.2                              | 5.3 $\pm$ 2.9           | 0.247        |
| 3+                                 | 3.5 $\pm$ .3                               | 2.9 $\pm$ 0.4           | 0.036        |
| 4+                                 | 1 $\pm$ 1.3                                | 5.2 $\pm$ 8.4           |              |
| 4+                                 | 1(1-1.3)                                   | 1(1-2.7)                |              |
| Serum creatinine, mg/dl            |                                            |                         |              |
| Albumin, gm/dl                     |                                            |                         |              |
| Bilirubin, mg/dl                   |                                            |                         |              |
| INR                                |                                            |                         |              |

AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BBs, beta blockers; BP, blood pressure; CCBs, calcium channel blockers; HB, hemoglobin; INR, international normalized ratio; PLT, platelet; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; WBC, white blood cells.

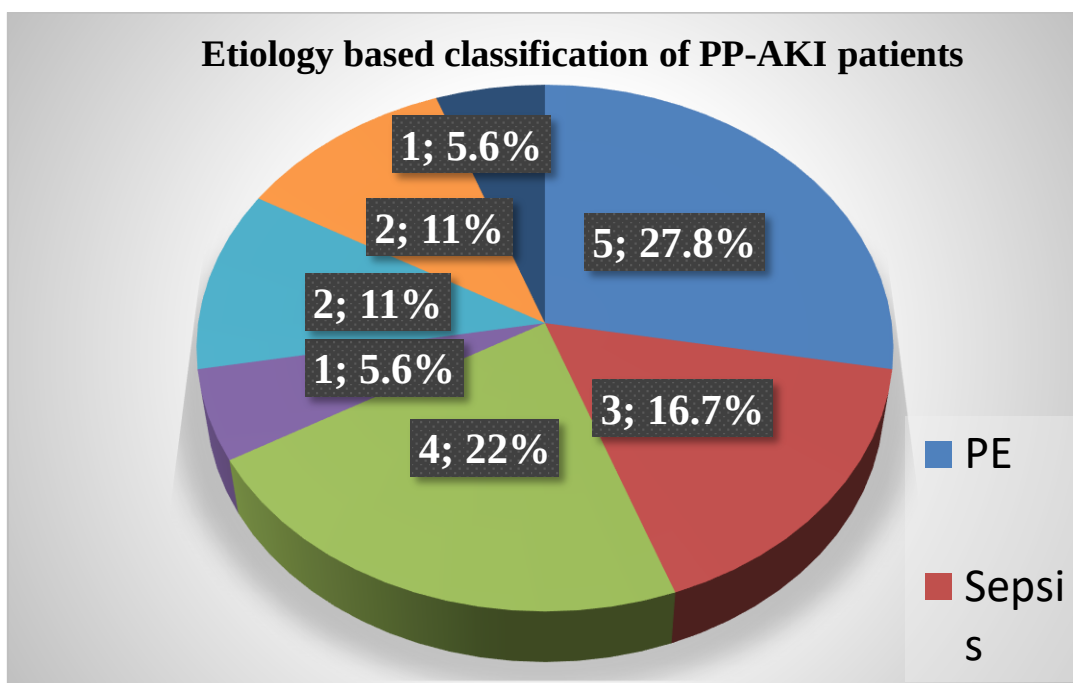


Figure 1: Etiology based classification of postpartum AKI patients.

## Discussion

PR-AKI occurring either intrapartum or immediately following delivery is relatively common. Coles et al. 2021 reported that PR-AKI occurring in 1.5 % of deliveries [13]. Additionally, PR-AKI complicated 1.78% of total delivery in the third trimester of pregnancy in a recent study in developing country [9]. According to the literature, approximately 75% cases of PR-AKI occur during the late third trimester and in the early postpartum. Additionally, the hypertensive complications of pregnancy, particularly PE and/or HELLP, are the leading causes of PR-AKI in most parts of the world, including developing countries [14]. In our locality, PP-AKI represented 32.5% among all causes of PR-AKI in a previously published cohort with postpartum hemorrhage and preeclampsia representing the main causes [15]. PE was the most common etiology of AKI among our PP-AKI patients with a percentage of 40%. On the contrary, in a study from India conducted by Krishna and his colleagues, the mean duration of gestation was 27 weeks, and the most common cause of PR-AKI in their study was sepsis either sepsis after abortion, after medical termination of pregnancy , and puerperal sepsis [16].

Postpartum haemorrhage has been identified as a relatively common cause of PR-AKI [17, 18]. Coles et al. 2021 study reported PPH in 71 % of their PR-AKI women with 21 % of women having an estimated blood loss at delivery of 1.5 L or greater [13]. A retrospective Canadian study examining women who developed AKI in pregnancy that required dialysis showed that in 18 % of cases women had a pregnancy complicated by PPH [25]. Our study is single center study, where there is high incidence of preeclampsia in our geographical area; this can explain the low prevalence of PPH in our PR-AKI cases.

In the study conducted by Godara et al. 2014, the most common age group affected by AKI was 20-25 years [19]. In the current study, our PR-AKI patients were older with mean age  $27.17 \pm 6.3$  years. In accordance with our results, the median age of women hospitalized due to PR -AKI in the United States from the 2006 to 2015, was 28 years [20]. As well as, the mean age in a study from India involved 98 of PR-AKI cases who required dialysis, was also 28 years [16]. Shah and his colleagues reported that diabetes was associated with a 4.4-fold higher risk of AKI during pregnancy [20]. Oppositely, none of our patients had diabetes. HTN and chronic kidney disease were detected in 27.8%, and 16.7% of our AKI group respectively, which are strong risk factors for AKI.

PR-AKI is associated with serious maternal and fetal complications. A meta-analysis of Liu et al. 2017 on PR-AKI, reported that 2.4% of women with AKI during pregnancy progressed to ESRD and needed long-term dialysis [12]. Shah et al. 2020, reported that PR-AKI was associated with a 13. 5-fold risk increase for in-hospital mortality. In the study of Godara and his colleagues, 15.79% of PR-AKI patients expired. Of note, ~~that~~ the mean serum creatinine in Godara et al. study was  $6.5 \pm 2.5$  mg/dl [19]. On the other hand, a study from Casablanca has reported maternal mortality in 9.1% of their patients [21]. Erdemoglu et al reported on 75 women with pregnancy-related AKI from Turkey, and their maternal mortality rate was 10.6% [22]. PP-AKI is a serious condition that has severe effects on the mother in the near and far future, which requires further studies for the epidemiology of PP-AKI and its possible etiology and risk factors.

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