ORIGINAL ARTICLE

An Evaluation of Risk Factors Associated with Pregnancy Related Acute Kidney Injury in Women Admitted to the High Dependency Care Unit at Women and Newborn Hospital, Lusaka-Zambia

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ABSTRACT

Objective: To evaluate factors associated with Pregnancy-related Kidney Injury (PRAKI) in women admitted to high dependency care unit at Women and Newborn Hospital in Lusaka, Zambia

Methodology: This was an unmatched case-control study conducted in the high-dependency care unit at Women and Newborn Hospital in Lusaka. Study participants were recruited consecutively by convenience sampling. Participants' medical records were reviewed to capture serum creatinine levels; while a structured questionnaire was administered to eligible and consented study participants to capture data on sociodemographic, obstetric, and medical factors. Serum creatinine levels above 84µmol/l were used as criteria for classifying PRAKI. Excel was used for data cleaning and Stata v13 used for analysis. Descriptive statistics were done for all variables followed by univariate and multivariable logistic regression to determine association. 95% CI was used and p value of <0.05 was considered significant.

Results: The study comprised of 185 study participants, split into 85 women with PRAKI (cases) and 100 women without PRAKI (controls). The median age was 29 years with 11years interquartile range. 75.3%of the study participants were in marriage relationships. Pre-existing hypertension was the most prevalent medical condition in both the cases (51.8%) and the controls (38%). Sickle cell disease was much less common at 1.2% in cases and 8% in controls. Among the obstetric conditions, preeclampsia was the most common condition at 77.6% and 60% in cases and controls respectively. Eclampsia was found in 38.8% of cases and 11% of controls. Sepsis was least common at 4.7% of cases. This study found that obstetricfactorssuch as eclampsia (AOR = 5.12, 95% CI [2.14 – 12.23]; p≤0.0001), preeclampsia (AOR = 2.46, 95% CI [1.12 – 5.39]; p = 0.025), and postpartum haemorrhage were associated with the development of PRAKI. Medical conditions were not associated with PRAKI.

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Conclusion: Obstetric factors such aseclampsia, preeclampsia, andpost-partum haemorrhage were found to be significantly associated with the development of PRAKI among pregnant women studied.

INTRODUCTION

Pregnancy-related acute kidney injury (PRAKI) is an acuterenaldys function that occurs in pregnancy orpuerperium. It is characterised by abrupt decrease in kidney function leading to accumulation of nitrogenous waste products and other uremic toxins.[1,2] It occurs between 6% and 55% of pregnant women and overall, is one of the most common causes of acute kidney dysfunction, contributing 20% – 40% of all cases.[3] PRAKI is associated with development of chronic kidney disease and end-stagerenaldisease, hypertension, cardiovascular disease, maternal mortality and poor foetal outcomes including still births and perinatal mortality.[4,5]

Globally, there has been a dramatic decrease in the incidence of PRAKI over the past 50 years. This reduction, however, has not been uniform worldwide.[6] Indeveloped nations, the incidence is 1%-2.8% while in developing countries PRAKI is still frequent and its incidence varies considerably from country to country.[7,8]A study in Morocco found PRAKI rates of 66 per 10,000 deliveries[9] while in Malawi it was 8.1%.[10] Although the incidence of PRAKI has significantly decreased in the developed world, it remains a serious public health problem in developing countries where there is limited access to prenatal care and to abortion services.[5,11]A number of aetiological factors are involved in the pathobiology of PRAKI, including obstetric factors and medical factors. Some of the obstetric and medical factors includes epticabortion, puerperalsepsis, preeclampsia, postpartum haemorrhage, gestational hypertension, heart failure, hyperemesis gravidarum, and renal disease.[12,10]In high income countries, the causes of PRAKI are slightly different and include pregnancy-specificdiseases like preeclampsia/eclampsia (PE/E), haemolysis/ elevated liver enzymes/low plateletcount (HELLP) syndrome, thrombotic micro-angiopathy of pregnancy(P-TMA), haemorrhage by abrupt ionplacentae, and acute fatty liver of pregnancy (AFLP).[13]

The maternal and foetal morbidity and mortality as a result of PRAKI is largely due to potentially preventable complications and complete renal recovery is achievable with appropriate and timely management.[14] Knowledge of the risk factors underlying PRAKI in developing countries is limited to enable appropriate triage and targeting of scarce resources.[15]PRAKI is more common in under-resourced countries, including Zambia, where it is less well studied. The difference in the access to health care among the rural and urban populations in Zambia could be recognised as an important factor associated with poor maternity out comesamong the impoverished rural women. This study was aimed at evaluating the socio-demographic, medical, obstetric and gynaecological risk factors associated with the development of PRAKI in women with and without the disease. The study was conducted over a period of six months at Women and Newborn Hospital (WNH) in Lusaka city of Zambia.

METHODS

This was an unmatched case-control study conducted in the high-dependency care unit (HDU) in the WNH for six months' duration between 1st February and 31st July 2020. WNH is a tertiary level hospital and a referral centre for maternity and gynaecological complications. It has a high dependency unit that is essentially the hospital's intensive care with six beds for critical nursing care, two of which are equipped with ventilation support equipment. Adjacent to the intensive care is the step-down care unit with a further six beds for high dependency nursing care. Acute or chronic kidney dysfunction at any stage of pregnancy forms a hospital criterion for admission to this ward. Study participants were recruited consecutively by convenience sampling. A case was defined as a pregnant woman at any gestational age or a woman in puerperium with serum creatinine equal to or above 84µmol/l; while those with creatinine levels

less than 84µmol/l were categorized as controls. Participants' medical records were reviewed to capture serum creatinine levels while a structured questionnaire was administered to eligible and consented study participants to capture data on sociodemographic, obstetric, and medical factors. Serum creatinine levels above 84µmol/l were used as criteria for classifying PRAKI. The questionnaire was administered in a face-to-face interview by four specifically trained qualified midwives who worked in the HDU ward on different shifts to ensure 24hours coverage. Where necessary, verification and additional information was obtained from patient medical files and collateral history from elatives. Participants for recruitment were selected based on the attending obstetrician's clinical diagnosis of acute kidney injury.

DATA ANALYSIS PLAN

The raw data were cleaned and coded in Excel and was then exported to Stata/SE version 13 (STATA Corp. College Station, Texas, USA) for analysis. Binary and categorical data were summarized as frequencies and expressed in percentages. Chi-squaretest was used for categorical variables where the frequencies were above 5, below that Fisher's exact test was used. For continuous variables such as age, a normality test using Shapiro-Wilk test was done to determine whether the age was normally distributed or not. Since the age was not normally distributed, Mann–Whitney U test was used, and median and interquartile range were reported. Univariate conditional logistic regression analysis was conducted to determine acrude (i.e., unadjusted) association between the outcome (PRAKI) and one independent variable. To identify factors associated with development of PRAKI after adjusting for confounders, multi variable conditional logistic regression was conducted with probability of variables being included in the final model set at 20%.Oddsratio was computed to estimate the strength of association. Confidence interval of 95% was used and *p* value of less than 0.05 was considered significant.

RESULTS

Descriptive statistics

Altogether 185 women were enrolled in this unmatched case-control study with85 cases and 100 controls. The median age of the women was 29 years with interquartile range of 11 years and more women fell in the age range of 30 to 34 years (25.1%). About two thirds lived in the high-density areas of Lusaka and majority of the study participants (75.1%) were married. Pre-existing hypertension was the most prevalent medical condition in all the participants accounting for 44.3%. Sickle cell disease was much less common at 4.9%. Among the obstetric conditions, preeclampsia was the most common at 68.1% followed by eclampsia (23.8%). Sepsis was observed in 4 (2.2%) of all the women().

Proportions of Socio-demographic, Medical and Obstetric factors between cases and controls

PRAKI was more commonly diagnosed in women aged 25 – 34 years (27.1%), with median age of 29 years. Majority of the women were married in both cases and controls, (cases = 75%, controls = 75.3%) compared to those that were single (cases = 25%, controls = 24.7%), though this difference was not statistically significant (*p* = 0.963). Furthermore, majority of the women came from high residential areas of Lusaka (cases = 62.4%, controls = 60%). The most prevalent medical condition was pre-existing hypertension in both, 51.8% in the cases and 38% in the controls, though the difference was not statistically significant (p= 0.060). Although diabetesmellitus (DM) can frequently complicate kidney function, there was no apparent difference in the presence of DM in the cases and the controls (5.9% vs 6%). There was higher frequency of both pre-eclampsia (77.6%)and eclampsia (38.8%) in the women with PRAKI compared to 60% and 11% respectively in the controls. These differences were highly statistically significant (p = 0.010 vs <0.0001).Similarly, there was higher frequency of hyper-emesis gravidarum (18.8%) in women with PRAKI compared to 13% in the control group, a

difference which nevertheless was not statistically significant (p=0.278). Obstetric haemorrhage (both pre- and postpartum) was observed more frequently in women with acute renal dysfunction (34.1%) compared to 13% in those without. These differences carried high statistical significance (). Sepsis due to puerperal infection and/orunsafe abortion was only present in women with PRAKI (4.7%).

Table 1: Descriptive characteristics of the study participants (n = 185) with and without PRAKI

Variables	Frequency (n)	Percentage (%)	Median	IQR
Age in years, median (IQR)			29	11
15 – 19	26	14.1		
20 – 24	28	15.1		
25 – 29	46	24.9		
30 – 34	47	25.4		
≥35	38	20.5		
Residence				
Low density	7	3.8		
Medium density	65	35.1		
High density	113	61.1		
Marital status				
Married	139	75.1		
Single	46	24.9		
Medical conditions				
Diabetes mellitus	11	5.9		
Pre-existing **hypertension**	82	44.3		
HIV	25	13.5		
Malaria	27	14.6		
Sickle cell disease	9	4.9		
Obstetric factors				
Hyperemesis gravidarum	29	15.7		
Preeclampsia	126	68.1		
Eclampsia	44	23.8		
Antepartum haemorrhage	12	6.5		
Postpartum haemorrhage	30	16.2		
Sepsis(post abortion)	4	2.2		

IQR=Interquartile range; HIV=Human Immunodeficiency Virus

Table 2: Proportions of socio-demographic, medical and obstetric factors between cases and controls

Socio-demographicfactors			
Age categories (years)			0.211
" - "	13(13%)	13(15.3%)	
20 – 24	21(21%)	7(8.2%)	
25 – 29	23(23%)	23(27.1%)	
30 – 34	24(24%)	23(27.1%)	
≥35	19(19%)	19(22.4%)	
Maritalstatus			0.963
Married	75(75%)	64(75.3%)	
Single	25(25%)	21(24.7%)	
Residence			0.640
Lowdensity	5(5%)	2(2.4%)	
Mediumdensity	35(35%)	30(35.3%)	
Highdensity	60(60%)	53(62.4%)	
Medicalconditions			
Diabetesmellitus	6(6%)	5(5.9%)	0.973
Pre-existinghypertension	38(38%)	44(51.8%)	0.060
HIV	11(11%)	14(16.5%)	0.278
Malaria	12(12%)	15(17.6%)	0.278
Sicklecelldisease	8(8%)	1(1.2%)	0.031[f]
Obstetricfactors			
Hyperemesisgravidarum	13(13%)	16(18.8%)	0.278
Preeclampsia	60(60%)	66(77.6%)	0.010
Eclampsia	11(11%)	33(38.8%)	<0.0001
APH	3(3%)	9(10.6%)	0.036[f]
PPH	10(10%)	20(23.5%)	0.013
Sepsis(puerperal/postabortion)	0(0%)	4(4.7%)	0.043[f]

P-value for differences between cases and controls; Chi-square test for categorical variables; f=Fisher's exact test; PPH = post partumhaemorrhage; APH =antepartumhaemorrhage

Univariate logistic regression analysis of socio-demographic, medical and obstetric factors in relation to development of PRAKI

Univariate conditional logistic regression analysis showed that age was not associated with risk of developing PRAKI (p>0.05). The odds for PRAKI in single (unmarried) women were 1.02 (COR = 1.02, 95% CI [0.52-1.98]; p = 0.983) compared to married women although not statistically significant.

In this analysis, the women with DM appeared to be 2% less likely to develop the AKI compared to those without diabetes (COR = 0.98, 95%CI [0.29 – 3.33]; p = 0.973). This finding, however, was not statistically significant. Similarly, sickle cell disease appeared protective from PRAKI in this analysis (COR = 0.14, 95% CI [0.02 -1.12]; p = 0.063). This fallacy owes to the small numbers of sickle cell patients analysed in both the groups. Asanticipated, hypertensive disorders of pregnancy and obstetrichaemorrhage had higher odds for developing PRAKI showing high statistical significance ().

Multi variable conditional logistic regression analysis assessing variables for development of PRAKI

After univariate analyses for socio-demographic, medical and obstetric characteristics, variables with p-values less than or equal to 0.2 (20%) were selected for multiple conditional logistic analysis. In this analysis, only significant results were reported while adjusting for all other variables in the model. Women who had eclampsia (AOR =5.12,95% CI[2.14 – 12.23]; p<0.0001), preeclampsia (AOR =2.46,95% CI[1.12-5.39]; p = 0.025) and post-partum haemorrhage (AOR =4.29,95% CI[1.54 –11.89]; p = 0.005) were more likely tohave PRAKI compared to those without these conditions.

Table 3: Univariate conditional logistical regression of socio-demographic, medical and obstetric factors in relation to development of PRAKI

Variables	COR	95%CI	p-value
Socio-demographicfactors			
Age categories (years)			
15 – 19	Ref		
20 – 24	0.33	0.11-1.05	0.061
25 – 29	1.00	0.38-2.62	0.998
30 – 34	0.96	0.37-2.50	0.931
≥35	1.00	0.37-2.71	0.998
Maritalstatus(Single)	1.02	0.52-1.98	0.983
Residence			
Mediumdensity	1.36	0.31 -5.90	0.684
Highdensity	1.41	0.34 -5.91	0.637
Medicalconditions			
Diabetesmellitus	0.98	0.29 - 3.33	0.973
Pre-existinghypertension	1.57	0.97 -3.15	0.061
HIV	1.60	0.68 -3.73	0.281
Malaria	1.57	0.69 - 3.57	0.281
Sicklecelldisease	0.14	0.02 -1.12	0.063
Obstetricfactors			
Hyperemesisgravidarum	1.55	0.70 - 3.44	0.280
Preeclampsia	2.32	1.21- 4.43	0.011
Eclampsia	5.14	2.39 -11.02	≤0.0001
APH	3.83	1.00 - 14.63	0.050
PPH	2.77	1.22 - 6.31	0.015

COR=crude odds ratio; CI=confidence interval; Ref.=reference category; PPH=post partum haemorrhage;
APH= antepartum haemorrhage HIV =Human Immunodeficiency Virus

Table 4: Multivariable conditional logistic analysis for association between PRAKI and predictor

Variable	AOR	95%CI	*p*value
HIV	1.07	0.38 -3.01	0.906
SCD	0.20	0.02 -1.91	0.161
Hyperemesisgravidarum	1.70	0.56 -4.44	0.277
PPH	4.29	1.54 -11.89	0.005
APH	2.47	0.57-10.81	0.228
Eclampsia	5.12	2.14-12.23	≤0.0001
Preeclampsia	2.46	1.12-5.39	0.025

AOR=adjusted odds ratio; CI=confidence interval; HIV=Human Immunodeficiency Virus; SCD=sickle cell disease; PPH =post partum haemorrhage; APH= ante partum haemorrhage

DISCUSSION

This study found that eclampsia had the higher odds of development of PRAKI followed bypostpartum haemorrhage (PPH) and then preeclampsia(). ThiswasincontrasttoastudydoneinMoroccoin2013w herepreeclampsia was the mainrisk factor for PRAKI, followed by eclampsia.[9] Similarly, another Moroccan study two years later found that preeclampsia was the most common cause, then septic events and pregnancy haemorrhages.[16] On the contrary, a study done in India in 2008, found that puerperal sepsis was the major risk factor associated with development of PRAKI, followed by obstetric

haemorrhage.[17]Eclampsia was the commonest associated risk factor for PRAKI in this study possibly because of the high prevalence of preeclampsia in African women occurring in 10% of pregnancies, compared to a global average of 2%.[19] Risk factors for preeclampsia include black race, maternal anaemia and infections, multi-parity, and low socioeconomic status that are all highly prevalent in African women.[20,21] Preeclampsiais a multi system disorder with a nunclear pathogenesis but is a condition characterized by new-onsethypertension and proteinuria after 20 weeks' gestation.[22] In preeclampsia, there are haemodynamic derangements that result in decrease in renal plasma flow, glomerular filtration rate and vasoconstriction of renal vessels predisposing the kidney stoischaemic injury.

In Africa the major risk factors associated with PRAKI are sepsis, hyperemesis gravidarum and hypertensive disorders of pregnancy (these include eclampsia and preeclampsia).[14,18,10] Sepsisinthis study included both post abortion and puerperalsepsis. However, all the participants with sepsis in this study belonged to the cases and non in the controls, therefore this variable was dropped in logistic regression analysis.

In this study, PPH was associated with increased risk of developing PRAKI by four-fold. However, the results were not statistically significant for APH. In a study done in Canada, the results showed that PPH was the commonest risk factor for PRAKI.[24]PPH can lead to hypovolaemia due to hypoperfusion of the parts of kidneys and subsequent reduction in glomerular filtration rate. If the state of hypovolaemia is sustained, ischaemic injury to parts or all of kidney ultimately occurs.[23]

Pre-existing hypertension and diabetes mellitus though are linked to the pathophysiology of PRAKI, in this study association was not significant ($p>0.05$). However, the proportion of hypertension was more among the cases (51.8%) than the controls (38%).

In this study, Human Immunodeficiency Virus (HIV) was more common in the cases than in controls, although not statistically significant. Similarly (as HIV) Malaria was found to be more common among participants with PRAKI than controls in the current study. The likelihood of developing PRAKI in a participant who had malaria was 34% compared to participants that did not have malaria. In contrast, a study in Pakistan found malaria in only 2.3 % of patients with PRAKI.[25] According to WHO, the majority of cases of malaria happen in sub-Saharan Africa and pregnant women are at considerably higher risk of contracting malaria and developing severe disease.[26] Women are increasingly susceptible to malaria during pregnancy because *Plasmodium falciparum*, the most common parasite responsible for malaria avoids spleen clearance by binding to the placenta.[20]

Sickle cell disease in this study was surprisingly more common in the controls. In contrast, in a survey in United States found that PRAKI was more common among women with SCD 10(0.7%) ($p<0.0001$) compared to women without SCD.[27]Thiscouldbeduetoimprovementsinmedicalcareand management of SCD patients that has resulted in reduced morbidity and mortality associated with the condition. The other reason could be that SCD being a chronic non-communicable disease increases the likelihood and frequency of seeking qualified care resulting in less consequences such as those posed by PRAKI.[28] Repeated vaso-occlusive crises in multiple organs can lead to a number of complications including renal dysfunction, pulmonary hypertension and stroke among others.

CONCLUSION

This study found that the development of PRAKI was mainly associated with obstetric factors such as eclampsia, preeclampsia, and post-partum haemorrhage.

ETHICALAPPROVAL

For the conduct of this research, approval was obtained from the University of Zambia Biomedical Research Ethics Committee (UNZABREC, **REF. No. 312-2019)**,and National Health Research Authority (NHRA). Signed consent forms from all eligible participants were obtained prior to enrolment. Participants' information was kept

confidential throughout the study, and numbers were used instead of names.

CONFLICT OF INTEREST

We affirm that we did not have any conflict of interest during the execution of this study.

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