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Original Article

Incidence of Pregnancy-Related Acute Kidney Injury in a Low Resource Setting: A Prospective Study

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Abstract

Background: Pregnancy-related acute kidney injury (PRAKI) is a common cause of AKI globally. The incidence and burden of PRAKI are still high in low and middle-income countries (LMICs) especially in Africa due to limited access to optimal obstetric care, late diagnosis, and referral. The study aimed to determine the incidence and aetiologies of PRAKI among women in the peripartum period in two government hospitals in Nigeria.

Methodology: This was a prospective study where serum creatinine was measured among pregnant women presenting in labour at 0-hour, 6 hour, 12 hour, 24 hour, 48 hour and 7 days post-delivery. AKI was defined using the Kidney Disease Improving Global Outcome criteria. Binary logistic regression was used to determine predictors of PRAKI.

Results: The mean age of the 162 pregnant women who completed the study was 30.05±1.28 years. The incidence of AKI use was 22.2%. The aetiologies of PRAKI were obstetric haemorrhage (66.7%), eclampsia (19.4%), and sepsis (13.9%). Seventeen (47.2%) patients had Stage 1 PRAKI, 12 (33.3%) had Stage 2 PRAKI, while seven (19.4%) had Stage 3 PRAKI. Factors significantly associated with PRAKI were parity (p=<0.001), caesarean section (p=<0.001), excess blood loss (p=<0.001), and prolonged duration of labour (p=0.002).

Conclusion: PRAKI occurred in 1 out 5 pregnant women in the peripartum period. Obstetric haemorrhage, sepsis, and eclampsia which are preventable or treatable are common major aetiologies of PRAKI. PRAKI is more associated with multi-parity, caesarean delivery, haemorrhage, and prolonged duration of labour. Optimal ante-natal care, health education, and prompt diagnosis and management of obstetric complications will reduce the incidence in Nigeria.

Keywords: Pregnancy, Related Acute Kidney Injury, Aetiology, Peripartum

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Quick Response Code:

Introduction

Pregnancy-related acute kidney injury (PRAKI) is a common cause of AKI globally with a pooled incidence of 2% [1]. It is the second most common cause of AKI in Africa [2]. The global burden of PRAKI seems to be reduced due to the improvement in obstetric care over the years [3,4]. The incidence of PRAKI is relatively higher in the low- and middle-income countries compared with the high-income countries (4%-26% versus 1%-2.8%, respectively) [5]. However, recent reports showed an increasing incidence of PRAKI in high-income countries due to an increase in the population of women with high-risk pregnancies such as diabetes mellitus, hypertension, chronic kidney disease, and advanced maternal age [3,4]. This is made possible by advancements in technology, especially in the area of assisted reproductive techniques. The incidence and burden of PRAKI are still high in low and middle-income countries (LMICs) especially in Africa due to limited access to optimal obstetric care, late diagnosis, and referral [2].

The common causes of PRAKI are hypertensive disorders in pregnancies (HDP), obstetric haemorrhage, and infections [2,6,7]. These causes are preventable and treatable if proactive measures are taken by governments, policymakers, and health workers. PRAKI is associated with adverse consequences such as increased maternal and perinatal morbidity and mortality [2,6,7]. In Africa, reports showed that maternal and perinatal mortality rates associated with PRAKI were as high as 34.4% and 60.5%, respectively [2]. PRAKI is also a risk factor for chronic kidney disease [1,7].

Despite the high occurrence and adverse outcomes associated with PRAKI, there is still limited information on the epidemiology of the disease in Africa including Nigeria. The aim of this study was to determine the incidence, aetiologies, and risk factors of PRAKI in two government hospitals in Southern Nigeria. The information from this study will help to create more awareness about the problem and provide useful evidence-based information to guide practice and drive policies that will reduce the associated burden in Nigeria and Africa.

Methodology

This study was a prospective study carried out in two public tertiary health centres serving the host State and neigbouring States. The study recruitment was done over a period of 5 weeks between 10th March 2020 and 16th April 2020. All consenting booked and unbooked pregnant women presenting in labour with a baseline serum creatinine and pregnant women diagnosed with chronic kidney disease but with stable eGFR higher than 15ml/min/1.73m^2 were eligible for inclusion in the study. Those with end-stage renal disease, on renal replacement therapy, sepsis, and with a clinical diagnosis of AKI were excluded.

Sample size estimation

The sample size was calculated using the prevalence of PRAKI in 3rd trimester from a previous study by Sivakumar et al. [8] which was 16.9%. The estimated number of pregnant women who deliver in the labour unit of both hospitals was approximately 6000 per year (from the departments' statistics). Cochran's formula with correction for a population is less than 10,000 was used for sample size determination [9]. The minimum sample size after the inclusion of a 15% attrition rate was 173. Participants were recruited consecutively as they presented to the labour units of the respective hospitals.

Semi-structured interviewer-administered pro-forma was used to obtain relevant socio-demographic and clinical information. Socio-demographic information obtained included age, ethnicity, level of education, type of occupation, and religion. Clinical information obtained were parity, mode of delivery, duration of labour, presence of complications, and estimated blood loss. Systolic and diastolic blood pressure were recorded. 3ml of whole blood was collected in a lithium heparin bottle from study participants at 0hr, 6hrs, 12hrs, 24hrs, and 48hrs and 7 days post-delivery. Blood samples were separated, and the sera were

stored at -20^{o}c. Serum creatinine was determined using the ARCHITECT c4000 clinical chemistry analyzer manufactured by Abbot.

Definition of terms

***AKI*:** was defined using the KDIGO 2012 criteria as an increase in serum creatinine by at least 26.5umol/l (0.3mg/dl) within 48hours [10].

Baseline creatinine level: Defined as the lowest serum creatinine level during hospitalization or up to 30 days before hospitalization [11].

AKI was staged using the KDIGO 2012 criteria.

Pregnancy-related acute kidney injury (PRAKI): Pregnancy-related acute kidney injury was defined as acute kidney injury occurring during pregnancy, labour, delivery, and/or the postpartum period. PRAKI was defined with respect to serum creatinine as a clinical syndrome denoted by a decline in kidney function evidenced by an increase in serum creatinine to a level higher than 0.3 mg/dl (26.5 µmol/l) within 48 hours or an increase in serum creatinine to1.5 times baseline, which was known or presumed to have occurred within the prior 7 days.

Peripartum period: defined as the period short**ly** before, during and immediately after delivery

Septic abortion: A septic abortion refers to either a spontaneous miscarriage or medically induced termination of pregnancy that becomes complicated by the infection of the retained placental and/or fetal tissue manifesting as endometritis and parametritis [12].

Pre-eclampsia: defined as a systemic syndrome that is typically characterized by new-onset hypertension (BP ≥ 140/90mmHg) presenting > 20 weeks of gestation with more than 300mg of protein in a 24-hour urinary collection or 1+ (0.3g) on urine dipstick [13].

Eclampsia: defined as the occurrence of seizure in a patient with pre-eclampsia

HELLP's syndrome: defined as the presence of hemolytic anaemia, elevated liver enzymes, and low platelet in a patient with pre-eclampsia/eclampsia

Antepartum haemorrhage: defined as bleeding from or into the genital tract, occurring from 28 weeks of pregnancy and before the birth of the baby [14].

*Postpartum haemorrhage***: is** defined as the loss of more than 500 mL of blood after delivery [15].

Puerperal sepsis: defined as an infection of the genital tract occurring at any time between the onset of rupture of membranes or labour, and the 42nd day postpartum in which two or more of the following are present: Pelvic pain, Fever, i.e. oral temperature 38.5°C/101.3°F or higher on any occasion, abnormal vaginal discharge, abnormal smell/foul odour of discharge, delay in the rate of reduction of the size of the uterus (involution) (<2cm/day during the first 8days) (16).

Nulliparous: A woman who has never delivered, but may have had one or more pregnancies ending as abortions, ectopic or molar pregnancy before 28 completed weeks of gestation.

Primiparous: A woman who has had only one delivery. Note that a delivery refers to the birth of a foetus or foetuses that have reached the age of viability i.e. 28 gestational weeks in our environment.

Multiparous: A woman who has delivered more than once.

Statistical analysis

Data was collated and analyzed with the International Business Machines Statistical Package for Social Sciences (IBM-SPSS) version 22.0. Missing variables were minimal (less than 5%) and occurred randomly; they were excluded by the SPSS software as appropriate during analysis. Discrete variables were presented as frequencies and percentages. Continuous data were presented as means and standard deviation. Chi-square was used to compare categorical variables while student's t-test was used to compare means. The binary logistic regression analysis was not performed due to the small frequency of PRAKI cases. Statistical significance was taken at p-value < 0.05

Ethical Consideration

Ethical approval was obtained from the Health Ethics and Research Committee of the Delta State University Teaching Hospital, Oghara Delta State with reference number *DELSUTH/HREC/2019/070/0320*. A duly signed/thumb-printed informed consent or a recorded verbal consent was obtained from participants before they were recruited for the study.

Results

A total of 162 women completed the study giving a response rate of 93.6%. Fourteen women who insisted on being discharged after delivery did not complete the study. The mean age of pregnant women was 30±1.3years. The majority of the study participants were married (93.2%), ninety-seven (59.9%) had a primary level of education and 124(76.5%) had International Standard Classification of Occupation (ISCO) level 1, (Table I).

Table I: Socio-demographic characteristics of the respondents

Variable	Total N=162	PRAKI		P value
		No (n=126)	Yes (n=36)	
Age category (years.)	n (%)			
21-30	81 (50.0)	66 (52.4)	15 (41.7)	0.47†
31-40	69 (42.6)	51(40.5)	18 (50.0)	
>40	12 (7.4)	9 (7.1)	3 (8.3)	
Age† (mean± SD)	30.07±1.29	30.05±1.28	30.57±1.54	0.62§
Marital Status				
Married	151 (93.2)	120 (95.2)	31 (86.1)	0.07†
Single	11 (6.8)	6 (4.8)	5 (13.9)	
Religion				
Christianity	155 (95.7)	120 (95.2)	35 (97.2)	1.00*
Islam	7 (4.3)	6 (4.8)	1 (2.8)	
Level of Education				
Primary	97 (59.9)	75 (59.5)	22 (61.1)	0.66*
Secondary	49 (30.2)	37 (29.4)	12 (33.3)	
Tertiary	16 (9.9)	14 (11.1)	2(5.6)	
ISCO Occupational level				
Level 1	124 (76.5)	95 (75.4)	29 (80.5)	0.75*
Level 2	11 (6.8)	9 (7.1)	2 (5.6)	

Level 3	21 (13.0)	16 (12.7)	5 (13.9)	
Level 4	6 (3.7)	6 (4.8)	0 (0.0)	
Tribe				
Urhobo / Isoko	65 (40.1)	50 (39.7)	15 (41.7)	0.39*
Ijaw	37 (22.8)	31 (24.6)	6 (16.6)	
Itsekiri	23 (14.2)	19 (15.1)	4 (11.1)	
Ibo	16 (9.9)	13 (10.3)	3 (8.3)	
Yoruba	13 (8.0)	7 (5.5)	6 (16.6)	
Others	8 (4.9)	6 (4.8)	2 (5.6)	

*Fishers Test | †= Chi Square Test| §= Independent sample t-test

Out of the 162 participants, 87(53.7%) were multiparous, 105 (64.8%) were unbooked, 30 (18.5%) had caesarean section and 64(39.5%) had blood loss in excess of 1000mls. Thirty-six participants (22.2%) developed PRAKI. Factors significantly associated with PRAKI were parity (p=<0.001), caesarean section (p=<0.001), excess blood loss (p=<0.001), and prolonged duration of labour (p=0.002). (Table II)

Table II: Clinical characteristics of the study participants

Variable	**PRAKI**		**Total**	**P value**
	No (n=126)	**Yes (n=36)**	**N=162**	
Parity	**n (%)**			
0	52 (41.3)	6 (16.7)	58 (35.8)	<0.001†
1	9 (7.1)	8 (22.2)	17 (10.5)	
2	46 (36.5)	6 (16.7)	52 (32.1)	
3	19 (15.1)	16 (44.4)	35 (21.6)	
Booking Status				
Booked	50 (39.7)	7 (19.5)	57 (35.2)	0.06†
Unbooked	76 (60.3)	29 (80.5)	105 (64.8)	
PIH				
Present	6 (4.8)	5 (13.9)	11 (6.8)	0.06†
Absent	120 (95.2)	31 (86.1)	151 (93.2)	
Mode of Delivery				
Vaginal delivery	114 (90.5)	18 (50.0)	132 (81.5)	<0.001†
Caesarean Section	12 (9.5)	18 (50.0)	30 (18.5)	
Postpartum Haemorrhage				
Yes	22 (17.5)	22 (61.1)	44 (27.2)	<0.001†
No	104 (82.5)	14 (38.9)	118 (72.8)	
Puerperal Sepsis				
Yes	41 (32.5)	5 (13.9)	46 (29.7)	0.03†
No	85 (67.5)	31 (86.9)	116 (70.3)	
Eclampsia				
Yes	9 (7.1)	7 (19.5)	16 (9.9)	0.05†
No	117 (92.9)	29 (80.5)	146 (90.1)	
Blood Loss				
<500mls	72 (57.1)	3 (8.3)	75 (46.3)	<0.001*
500ml-1000mls	18 (14.3)	5 (13.9)	23 (14.2)	

>1000mls	36 (28.6)	28 (77.8)	64 (39.5)	
Blood Transfusion				
Yes	55 (43.7)	33 (91.7)	88 (54.3)	<0.001†
No	71 (56.3)	3 (8.3)	74 (45.7)	
Median Time to Delivery (Hrs)	15.5(12-17)	18(14-18)	16(13-18)	0.002§
Median Pulse Rate	88(82-89)	92(88-98)	88(85-90)	<0.001§
Median Systolic Blood Pressure (mmHg)	119(116-120)	119(110-130)	119(115-121)	0.49§
Mean Diastolic Blood Pressure (mmHg)	80.02±5.24	82.83±8.80	80±6.30	0.07†

*Fishers Test| †Chi Square Test| =Independent sample t-test| § = Mann-Whitney U test

The aetiologies of PRAKI were obstetric haemorrhage (66.7%), eclampsia (19.4%), and sepsis (13.9%). (Figure 1) Seventeen (47.2%) patients had Stage 1 PRAKI, 12 (33.3%) had Stage 2 PRAKI, while 7 (19.4%) had Stage 3 PRAKI. (Figure 2)

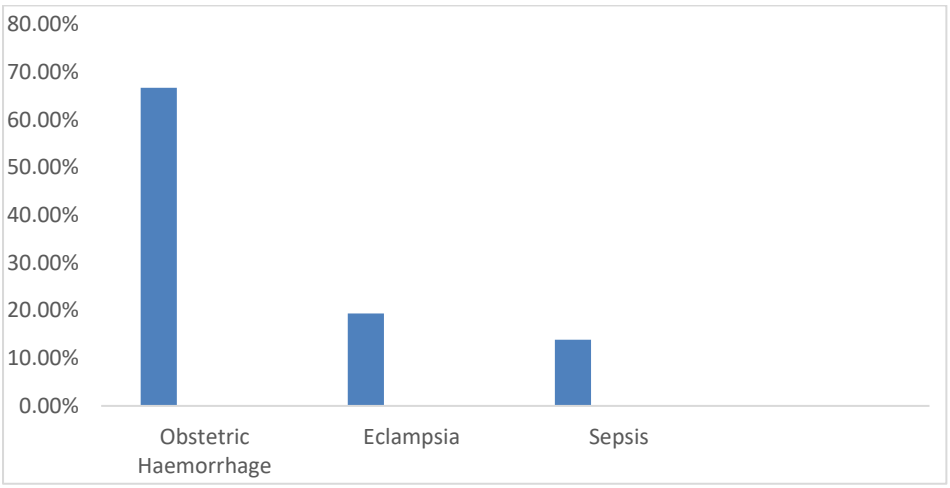

Figure 1: Aetiologies of PRAKI

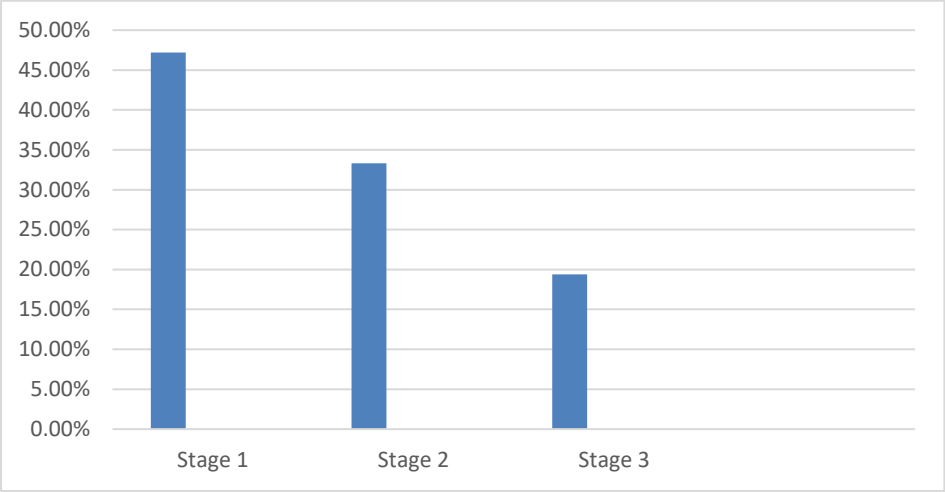

Figure 2: Stage of PRAKI

Discussion

This was a prospective study that determined the incidence, risk factors, and aetiologies of PRAKI among women in the peripartum period in two hospitals in Southern Nigeria. A fifth of pregnant women developed PRAKI, mainly caused by obstetric haemorrhage, sepsis, and eclampsia. Multiparity, caesarean section, excess blood loss, and prolonged duration of labour were associated with PRAKI while parity, increased blood loss, and caesarean delivery were independent risk factors.

The incidence of PRAKI in this study was 22.2%. This falls within 4-26% reported in low- and middle-income countries [5]. However, it is higher than the 8.0% reported by Cooke et al. [17] in Malawi, 8.6% reported by Ruggajo et al. [18]. in Tanzania, and 0.7% reported by Arrayhan et al. [19]. It is also higher than the 2% reported as the pooled incidence of PRAKI in Africa from a systematic meta-analysis involving 31 studies and 57,529, 841 participants [1]. The high incidence of PRAKI in the present study may be partly explained by better diagnostic accuracy because of the serial monitoring of kidney function that was done at 0hr, 6hrs, 12hrs, 24hrs, and 48hrs and 7 days post-delivery In addition, the wide differences in the incidence of PRAKI in the various studies may be partly explained by the differences in criteria used in the definition of AKI, socio-demographic and clinical characteristics of the study participants and quality of health services in the study area.

The mean age of the study population was 31 years which reflects average childbearing age in a female. This is comparable to the mean age of 29 years reported in a previous study done in Southwest Nigeria [29]. However, it is slightly lower than 26 years and 27 years reported in studies done in Somali and Northern Nigeria, respectively [21,22]. This difference may be related to the fact that the latter two studies were conducted among participants who were predominantly Muslims whose religion supports relatively early marriage. The proportion of females with PRAKI with low socioeconomic status according to the level of education and ISCO occupational level is higher, although not statistically significant. This is similar to some previous reports [20,22,23]. PRAKI was also more common in females who did not register for antenatal care. This is similar to a report of a systematic review and meta-analysis of PRAKI in Africa [2]. Previous studies have established an association between socioeconomic status and optimal antenatal care [24,25]. Those with lower levels of education are less likely to have optimal antenatal care which may predispose them to obstetric complications and the development of PRAKI. Adequate health education on the importance of optimal antenatal care will have

a positive impact on the reduction of the incidence of PRAKI especially in lower- and middle-income countries.

Obstetric haemorrhage was the most common aetiology of PRAKI in this study. Excess blood loss was also significantly associated with PRAKI. Significant blood loss during delivery could lead to hypovolaemia, reduced kidney perfusion, and pre-renal AKI if blood volume is not promptly and adequately replaced. Other common causes were eclampsia and puerperal sepsis. This is similar to reports from some previous studies [20-22]. However, the pattern of aetiologies of PRAKI is slightly different from some other reports that showed that hypertensive disorder of pregnancy was the most predominant cause. [2,17,19,26,27]. The major causes of PRAKI in this study are potentially preventable and treatable if diagnosed promptly; therefore, physicians should take proactive steps to prevent, promptly diagnose, and effectively manage the obstetric complications that could lead to PRAKI. Blood transfusion services should be improved to provide prompt supportive care and prevent PRAKI due to blood loss. Coincidentally, the common causes of PRAKI are largely responsible for high maternal mortality in Africa. Therefore, effective prevention and management of PRAKI will consequently lead to a significant reduction in maternal mortality.

There was a significant association between multiparity and PRAKI. This finding is like reports of some previous studies [20,27]. However, it is different from the findings of some other studies (26,28). Multi-parity may predispose to obstetric haemorrhage which is a common cause of PRAKI. Previous studies have reported that multi-parity is a risk factor for obstetric haemorrhage [29,30]. PRAKI was also more common in those who had caesarean delivery. This is similar to an earlier report by Adejumo et al. [20] This may be because operative delivery is more likely to be associated with blood loss which may significantly increase the risk of PRAKI. This explanation is supported by the findings from a systematic review which revealed that post-partum haemorrhage was a common complication of caesarean delivery [31]. In addition, those who have caesarean deliveries were more likely to have high-risk pregnancies ab initio which may predispose them to PRAKI

The limitation of this study is that other maternal and fetal outcomes were not reported, however, a follow-up study of these patients is currently ongoing. Also, there is presently no consensus criteria to define PRAKI, hence KDIGO criteria were used in this study. Despite its limitations, this study is one of the few prospective studies from the African region that involved serial assessment of kidney function over a period of one week in order to diagnose PRAKI.

In conclusion, the incidence of PRAKI is high in this study as seen in most developing countries. Obstetric haemorrhage, sepsis, and eclampsia which are preventable or treatable are still the major aetiologies of PRAKI. PRAKI is more associated with suboptimal ante-natal care, caesarean delivery, and low socio-economic status. Optimal ante-natal care, health education, and prompt diagnosis and management of obstetric complications will reduce the incidence of PRAKI in Nigeria.

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