PREGNANCY RELATED ACUTE KIDNEY INJURY AMONG WOMEN WITH PREECLAMPSIA AT KENYATTA NATIONAL HOSPITAL: RISK FACTORS, PROGRESSION AND PREGNANCY OUTCOMES

A Research dissertation submitted to the University of Nairobi, department of Obstetrics and Gynaecology in part fulfilment of the requirements for the award of the degree in Master of Medicine in Obstetrics and Gynaecology

UNIVERSITY OF NAIROBI

2021

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DECLARATION

This dissertation is my original work, under the guidance of my supervisors, towards the degree in Master of Medicine in Obstetrics and Gynaecology and has not been submitted for the award of a degree in any other university or published elsewhere. All references made to work done by others has been appropriately acknowledged and cited.

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CERTIFICATE OF AUTHENTICITY

This to certify that this dissertation is the original work of Dr Nyawira Wahome Ng'ayu, who is a Master of Medicine student, registration number H58/87288/2016, in the Department of Obstetrics and Gynaecology University of Nairobi. This study was conducted under the supervision of Dr Onesmus Gachuno and Prof Joshua Kayima. It has not been presented in any other university for the award of a degree.

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DEDICATION

I dedicate this dissertation to the Lord Almighty and then to my parents, Godfrey Wahome Ng'ayu and Alice Muthoni Wahome.

To God who has given me life and breathe and the opportunity to do this work.

To my dear parents who have laid the foundation and path for who I am today.

ACKNOWLEDGEMENTS

My deepest gratitude goes out to my supervisors, Dr Onesmus Gachuno and Professor Joshua Kayima for the tireless work of guiding my thoughts and progress throughout this study; all this with utmost patience, and readiness in giving off your time.

My sincere appreciation goes out to Dr Nelly Mugo and Professor Muia Ndavi who helped me make sense of the spaghetti of thoughts and ideas in my head, and statistical quagmires I often found myself in especially in the early stages of this research process. I am so grateful for your valuable input.

I could not have produced this work without the help of my research assistants who helped me gather data (Beatrice Ngillah, Lewis Olweywe, Labour Ward Midwives Doris Kirito, Wambui Gakuo, Fridah Oindo, Sally Ngotho), the Lab technologists (Zachary Gitonga, Cyril Lukano, Andrew Obura) who examined numerous urine samples and my statistician Dr Alex Mwaniki who's readiness, professionality and efficiency was so welcomed especially at the tail end of this research process.

To my dear father Dr Godfrey Wahome Ng'ayu whom I greatly respect and admire, you have encouraged me constantly (each conversation with you beginning with my research progress) and for funding my endeavors.

Lastly to my dear husband Patrick G. Macharia for financing this project, supporting me in your quiet solid way, and accepting to have a doctor for a spouse. I am forever thankful.

LIST OF ABBREVIATIONS AND ACRONYMS

AKI – Acute kidney injury
ACR – Albumin creatinine ratio
AER – Albumin excretion rate
ALT – Alanine aminotransferase
AKIN – Acute kidney injury network
APH - Antepartum Haemorrhage
ARV – Antiretroviral
ART – Assisted reproductive technology
AST- Aspartate transaminase
BP – Blood pressure
CKD – Chronic Kidney Disease
DB – Direct Bilirubin
DBP – Diastolic blood pressure
DIC – Disseminated intravascular coagulation
EOPE – Early onset preeclampsia
FSB – Fresh still birth
GDM – Gestational diabetes mellitus
GFR – Glomerular filtration rate
GH – Gestational hypertension
HELLP – Haemolysis elevated liver enzymes and low platelets
HIV – Human Immunodeficiency Virus
HLOE – Highest level of education
HCO3 – Bicarbonate
ICU – Intensive Care Unit
ISN - International Society of Nephrology
KDIGO – Kidney Disease Improving Global Outcomes
LDH -Lactate dehydrogenase
LFT – Liver function test
MSB – Macerated still birth
NKD – No kidney disease
NICU- Neonatal Intensive Care Unit
PE – Preeclampsia
PPH - Postpartum Haemorrhage
PrAKI - Pregnancy related acute kidney injury

RIFLE – Risk, Injury, Failure, Loss, End stage
RRT – Renal Replacement Therapy
TB – Total Bilirubin
SCr – Serum Creatinine
SBP – Systolic blood pressure
SPSS - Statistical Package for Social Science
UEC – serum Urea, Electrolytes and Creatinine

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OPERATIONAL DEFINITIONS

PREECLAMPSIA

Preeclampsia is defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) as new onset Hypertension after 20 weeks gestation with any of the following(1,2):

- proteinuria
- maternal end organ dysfunction including renal insufficiency, liver involvement, neurological manifestations, haematological derangements
- uteroplacental insufficiency

For purposes of this study, Preeclampsia will be defined and identified by the presence of Hypertension with proteinuria, and where Hypertension is classified as having SBP ≥ 140mmHg or a DBP ≥ 90mmHg. Other important definitions as per ISSHP used in this study, within the spectrum of hypertensive disorders of pregnancy are detailed below. Significant proteinuria will be taken as a 2+ positive dipstick urinalysis(1).

Early and Late onset preeclampsia.

The occurrence of preeclampsia before 34 completed weeks of pregnancy is considered early onset. Thereafter, preeclampsia is termed late onset(2).

Gestational hypertension

New onset hypertension after 20 weeks of gestation without the occurrence of target organ damage namely: proteinuria, haematological or biochemical derangements, and with no consequence to the growth of the foetus.

HELLP

This is the occurrence of haemolysis (raised total bilirubin concentration ≥ 20.5µmol/l), elevated liver enzymes (raised transaminases to twice the upper limit of normal or AST ≥ 70U/l) and low platelets (< 100 × 10^9/l) and considered as part of preeclampsia disease(2,3)

PrAKI

Pregnancy related AKI is defined in 3 ways as per KDIGO, assuming a normal GFR of 75mls/min per 1.73m^2(4)

- either by a rise in SCr of greater than or equal to 26.5 µmol/l (0.3mg/dl) within 48 hours; OR
- rise in SCr by 1.5 times of baseline known or presumed to have occurred within prior 7days; OR
- having a urine output of less than 0.5ml/kg for at least 6 hours

Serum creatinine levels above 90micromol/l will be regarded as abnormal, as per ISSHP guidelines(1).

CHRONIC KIDNEY DISEASE

The definition of CKD is based on that provided by KDIGO guideline which is the presence of a structural or functional kidney abnormality for greater than 3 months duration, and which has bearings on an individual's health. This is informed by the following parameters in the table overleaf (4,5).

Table 1

Definition of CKD, KDIGO Guideline*(5)*

Markers of kidney disease (one or more)	Albuminuria (AER≥ 30mg/24 hours; ACR ≥30mg/g {3mg/mmol})
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR < 60ml/min/1.73m^2 (GFR categories of G3a-G5)

Postpartum haemorrhage

Blood loss in excess of 500mls occurring within the first 24 hours after delivery(6).

Anaemia

Anaemia in pregnancy is defined by a haemoglobin concentration is < 11.0g/dl(7).

Preterm delivery

Live birth before 37 completed weeks of pregnancy(8).

Neonatal period(9)

This is the period between 0 to 28 days of life. It is divided into early neonatal period (day 0 to day 7 of life) and late neonatal period (day 7 to day 28 of life).

Perinatal Period(9)

This is the period between 22 weeks gestation up to 28 days of life.

Renal recovery rate

This is the proportion of PrAKI patients with resolution of renal function at the time of discharge or end of study period.

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ABSTRACT

Background: Pregnancy related acute kidney injury (PrAKI) is a global problem affecting mothers in varying incidences. PrAKI contributes 7-52% of AKI cases. Majority of PrAKI cases are in resource poor countries where access to antenatal care is limited especially in rural areas and where unsafe delivery practices occur. These pregnancies suffer a significantly higher risk of maternal and neonatal mortality and morbidity than in a normal pregnancy. There is an added risk of developing CKD in the long term. Information on the burden of disease of PrAKI in our local setting is scarce. Less is known of the risk factors that contribute to the occurrence of PrAKI, which is one of the hallmarks of the AKI management pathways proposed in the 0by25 initiative: risk assessment. This study aims to identify a set of risk factors that would guide patient stratification, early identification, and eventual early treatment of women with PrAKI with the hope of improving their health and pregnancy outcomes.

Study Objective: To determine the risk factors for pregnancy related acute kidney injury amongst women with preeclampsia and describe their pregnancy outcomes at Kenyatta National Hospital

Methodology: This was a prospective cohort study conducted at the Kenyatta National Hospital Obstetric Units involving 196 patients admitted with preeclampsia. Patients were identified and selected through Consecutive sampling method and enrolled upon consent. Patients with preeclampsia and AKI, n=47 were compared to patients with preeclampsia only, n=149. Information was collected through a data extraction form and urine samples of patients obtained at enrolment. Data was analysed and with STATA and R software. Chi-square analysis and Odds

Ratio were calculated to determine the differences in demographic, clinical data, urine microscopy, pre-defined risk factors for PrAKI and the pregnancy outcomes between the two groups. A p value < 0.05 was considered significant in determining associations.

Results: The mean age of patients was 29.6 years amongst PrAKI group versus 30.2 amongst the non PrAKI group. Significant risk factors for PrAKI were a lower gestation age of < 28weeks (OR 4.2, 95% CI: 1.2-14.5), fewer antenatal visits (OR 2.6, 95% CI: 1.2-5.5), thrombocytopenia of $<50\times10^9$/l) (OR 10.1, 95% CI: 4.3-24.1) and HELLP syndrome (OR 8.5, 95% CI: 4.0-17.9). Patients with PrAKI were more likely to undergo vaginal delivery and have persistent elevated blood pressure (>140/90) at discharge (SBP>140mmHg OR 2.1, 95% CI: 1.0-4.4 and DBP>90mmHg OR 2.0, 95% CI: 1.0-3.9). Perinatal outcomes were significantly adverse across all variables examined (perinatal mortality, birth weight, Apgar score at 5 minutes and new-born unit admission). Patients with persistently elevated serum creatinine at the end of the study had stage 2 and 3 AKI. The renal recovery rate was 44%. On multivariate analysis, early onset preeclampsia and severe thrombocytopenia were strongly associated with PrAKI and had the greatest effect on neonatal birth weight.

Conclusion and recommendation: PrAKI was significantly associated with poor antenatal attendance, lower gestational age, severe thrombocytopenia and HELLP syndrome and had worser perinatal outcomes compared with non-PrAKI patients. Partial renal recovery was seen in patients with advanced AKI stages. Further investigation on the long-term outcomes of PrAKI is needed.

1.0 INTRODUCTION

Acute kidney injury in pregnancy is a global problem affecting pregnancies in varying incidences, with the greatest burden seen in developing countries. Pregnancy related Acute Kidney Injury (PrAKI) contributes between 5-27% of all cases of Acute Kidney Injury (AKI) in Africa(10). The same was observed by Were (1985) who found PrAKI cases made up 34% of patients seen by the Nephrology team at Kenyatta National Hospital(11).

In 2018, The World Kidney Day campaign was centred on the growing concern for women's renal health, captured in their theme, "Kidney's and Women's Health: Include, Value, Empower"(12). Study Reviews generated from this campaign, highlighted the increasing pool of data describing the burden of disease that an altered kidney function poses on women who make up at least 50% of the world population. The reviews also highlighted the gap in access to education and health care between females and males, the presence of weak diagnostic and follow up programmes for women affected by kidney disease, and the insufficient data on the long-term health outcomes of women who are affected by AKI associated with pregnancy(13,14).

The International Society of Nephrology (ISN) propose use of the 5R approach to achieve their 0by25 Initiative, which aims to decrease the burden of AKI by 2025 particularly in low and medium resource countries. The 5Rs, include: risk assessment, recognition, response, renal support and rehabilitation(15). This strategy of risk assessment for AKI is also put forward in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines of 2012(4). This study hopes to address this first part of the management of AKI in identifying important risk factors that can be used to screen patients allowing for early recognition and response, to

receive timely renal support and rehabilitation, to avert preventable deaths from reversible causes of AKI that are prevalent in our setting.

2.0 LITERATURE REVIEW

2.1 Epidemiology of PrAKI

In the last 5 decades there has been a decreasing trend in the incidence of PrAKI by a factor of up to 5 in developed countries(16). The number of cases of PrAKI per 10,000 deliveries was 2.7 in Canada, 8 in Brazil, 11 in China, 66 in Morocco, 116 in Malawi and 109 in India, from studies published between 2012 and 2018(16–21). Unpublished data from a study that is first of its kind in Kenya looking at PrAKI, found an alarming incidence of 302 cases per 10,000 deliveries(22). Despite the downward trend, these numbers are still high in resource poor countries and its occurrence is associated with significant maternal and neonatal morbidity and mortality. This finding has been attributed to lack of antenatal care especially in rural areas, poor health care systems and the occurrence of unsafe delivery practices(16,23).

2.2 Causes of PrAKI

Globally, preeclampsia is the most common cause of PrAKI, with reported proportions of 40-80%(16–20), followed by postpartum sepsis and haemorrhage (ante/postpartum) (17,19,24–26). Availability of safe abortion services has reduced the rates of PrAKI from sepsis. In countries without access to safe abortion services, post abortal sepsis was the 2nd commonest cause of PrAKI, followed by haemorrhage(25,26). A meta-analysis done by Dwomoa et al looking at community acquired AKI in adults in Africa found the leading causes of PrAKI to be the syndrome of Haemolysis, Elevated Liver Enzymes and Low Platelets (HELLP), preeclampsia/eclampsia and peripartum haemorrhage(10). Bekele et al in Ethiopia

(2017) considered PrAKI patients requiring dialysis and found that 74% of cases were a result of preeclampsia or eclampsia, majority of whom (85%) had HELLP syndrome(25). Similarly, Cooke et al (2018) in Malawi, found that 73% of obstetric patients identified to have AKI had preeclampsia/eclampsia. In their study, the incidence of AKI in pre-eclampsia was 12% versus 4.3% in other obstetric patients, and this association was significant.

Across the globe, the same predominance of hypertensive disorders as a cause of PrAKI was observed. Mehrabadi et al conducted a population based retrospective cohort study in Canada and found an increase in the incidence of PrAKI from 1.66 to 2.68 per 10,000 in the year 2003-4 and 2009-10. The greatest proportion of these patients had hypertensive disorders of pregnancy. The increase was restricted to patients with hypertensive disorders, and was statistically significant amongst the group with gestational hypertension with proteinuria (preeclampsia)(21). The reason for the rise in incidence was unclear in this study, however, Rao reported on an increase in disease surveillance, difference in coding for AKI during this study period, and older maternal age which comes with added maternal risks as potential reasons for the change(26). Picolli et al (2018) have also reported findings that show an increase in PrAKI from PE in mothers who have conceived with the aid of ART(13). This data is summarised in table 2 on the following page.

Table 2

Epidemiology of PrAKI

Reference	Country	PrAKI incidence /10000 deliveries	AKI by disease aetiology (%/AKI)			Maternal mortality with AKI (%)	Author, Year, Journal
			PE	Sepsis	Haemorrhage		
(21)	Canada	2.68			Not Available	2.9	Mehrabadi et al, 2014. BMJ
(18)	Brazil	8	PE 42.1 HELLP 32.4	Sepsis 14.5	APH (abruptio) 9.1	30.9	Silva et al, 2009 Arch Gynecol Obstet
(16)	China	11	PE & E 49.2 HELLP 6.4		PPH 13.8	13.6	Liu et al, 2017 Internal Medicine
(19)	Morocco	66	PE 66.6		APH/PPH 25%	NA	Arrayhani et al, 2013 ISRN Nephrology
(27)	India	277	PE + E 46.9 HELLP 6.8	Sepsis 25.8	APH 8.3 PPH 21.2	6	Prakash et al, 2018 Journal of Nephrology
(17)	Malawi	116	PE + E 73.1	Sepsis 11.5	APH 11.1	No mortality found	Cooke et al, 2018 BMC Nephrology
NA: not available, P/E: pre-eclampsia, E: eclampsia, APH: antepartum haemorrhage, PPH: postpartum haemorrhage, HELLP: haemolysis, elevated liver enzymes, low platelets							

2.3 Risk factors for PrAKI

Studies describing PrAKI are recent, occurring in the last one decade. Most are descriptive cohorts to determine the incidence, aetiology and outcomes of pregnancies complicated by AKI; a few of which are African. There are 2 studies in Kenya, one is ongoing and another published, both of which have considered AKI amongst general obstetric patients(22).

Few studies have been done on risk factors peculiar to PrAKI. Risk factors may be considered into 2 broad categories as per KDIGO guideline, that of exposures and susceptibilities. A patient may have a certain exposure that may lead to AKI. For instance, the occurrence of preeclampsia spectrum of disorders carries a certain risk of AKI. Whilst an exposure may confer a quantifiable risk, patient specific factors will make them susceptible to developing AKI which include, advanced age, female gender, black race, dehydration or volume depletion, Chronic Kidney Disease (CKD), Chronic illness of heart, lung and liver, Diabetes Mellitus (DM), anaemia and

cancer. The exposures listed in the KDIGO guideline for the general population include sepsis, critical illness, circulatory shock, burns, trauma, nephrotoxic drugs, radiocontrast agents and several others(4).

Cooke et al used the following specific combination of exposures and susceptibilities as risk factors and which were present in 7.3% (26/354) of patients in their study: gestational hypertension, preeclampsia/eclampsia, sepsis, antepartum haemorrhage (APH), postpartum haemorrhage (PPH), heart failure and renal failure, DM, age, Human Immunodeficiency Virus (HIV) positive status as well as antiretroviral (ARV) and nephrotoxic therapy prior to recruitment. They showed that 12.2% of patients with preeclampsia spectrum of illness had AKI versus, 4.3% of AKI that occurred in pregnant women without preeclampsia. This difference was found to be significant (p=0.015). They had no mortalities in their study. This they attributed to early identification of renal dysfunction by using a lower threshold (82µmmol/l) and thus early management(17).

In a prospective observational study on women with preeclampsia done in South Africa, Nathan et al (2018) found a prevalence of 17.6% of AKI (272 patients out of 1547 women). A stepwise logistic regression model was used to determine significance of certain risk factors for PrAKI: maternal age, High BMI (≥ 35 kg/m^2), multiparity, low gestation at admission, highest systolic and diastolic BP at admission and during the study period and highest admission proteinuria on urine dipstick analysis. From these, highest systolic BP was found to be statistically significant for the occurrence of AKI amongst patients with preeclampsia(28). A follow up analysis on the same dataset done by Conti-Ramsden et al (2019) was done to investigate risk factors for PrAKI amongst patients with preeclampsia and the renal outcomes(29). They categorised risk factors to pre-admission and post-admission characteristics. Pre-admission characteristics included anaemia (Hb<9g/dl), HIV

infection, primiparous, parity, gravidity, chronic hypertension, previous history of hypertensive disorder of pregnancy, elevated BMI and age. Post-admission characteristics included gestation at admission, SBP and DBP on admission plus during hospital stay and urine dipsticks on admission(29). Their findings showed that maternal age plus a history of hypertensive disorder in the previous pregnancy were significant risk factors for AKI, with the latter being predictive of increasing severity of AKI (stage 2 or 3)(29).

A crosectional study done by Nguefack et al. in Nigeria (2018), looked at the differences between early onset preeclampsia (EOPE) and late onset preeclampsia in terms of their maternal-foetal predictors and short-term pregnancy outcomes. They found that the odds of AKI were 6.67 times higher in patients with EOPE (95% CI 1.73-25.73)(30).

Jonard et al (2014), in France found that HELLP syndrome occurring with PPH was a significant risk factor for AKI. They had considered various baseline characteristics included in the susceptibilities and exposures list mentioned above with the addition of pregnancy characteristics such as twin gestation, parity and caesarean versus vaginal delivery(31). The same dominance of hypertensive disorders as a risk factor for PrAKI was also found by Mehrabadi et al (2014). They found a strong association between PrAKI and pre-existing hypertension with proteinuria, gestational hypertension with significant proteinuria(preeclampsia), non-atonic postpartum haemorrhage, gestational oedema with proteinuria, sepsis and cardiac failure(21).

A prospective analytical study done in Morocco by Mjahed et al (2004) found the following exposures in patients with eclampsia to be significantly associated with AKI: DIC, HELLP, neurologic complications, abruptio placentae, aspiration

pneumonia and PPH, hyperbilirubinemia ≥12 µmol/l [OR 4.42, CI 1.54-12.68], uric acid > 5.9g/dl [OR16.5, CI 3.09 -87.9]. No significant association was found when severity of blood pressure and proteinuria on dipstick was considered(32). Still in Morocco, Bentata et al (2012) considered risk factors amongst PrAKI patients compared to pregnant women without AKI, and found that having a home delivery, severe hypotension, hyperbilirubinemia, oligoanuria, hyperuricaemia, thrombocytopenia, and hepatic cytolysis was statistically significant in favour of AKI. These risk factors have not been considered in our setting.

2.4 Urine Sediment analysis as a prognostic indicator in AKI

Several studies have demonstrated the use of urine sediment examination not only for diagnostic but also for prognostic purposes. Clinical end points such as worsening of renal function, increase in stage of kidney disease, need for renal replacement therapy (RRT) or even non recovery correlate significantly to higher scores when sediment scoring systems are used(33). A score is assigned for the presence of granular casts or renal tubular epithelial cells seen per high power field on light microscopy. More cells seen confers a higher score. The scores are tallied and compared to the AKI stage assigned to the patient at the time of sediment analysis. This was demonstrated by Perazella et al (2010) who found that an individual with a total score of ≥ 3 was more likely to have worsening renal outcome (increase in AKIN stage, need for dialysis, or death) versus those with a score of 0 from sediment examinations done at the first nephrology consultation(33,34). Studies on sediment analysis have been done on heterogenous population with varying pathophysiological causes of AKI. Cohorts include patients with prerenal and intrarenal failure from various causes, including sepsis, and not limited to an obstetric population. The urine sediment scoring system used, may be found in the appendix.

2.5 Mortality and Morbidity associated with PrAKI

Maternal mortality rates are higher in pregnancies complicated by AKI, particularly in developing countries. Conti-Ramsden in South Africa showed that amongst patients with preeclampsia, risk of death was 4.3 times higher in patients with AKI (95% CI, 1.6-11.4) (29). The proportions of deaths amongst pregnant women with AKI were found to be higher in PrAKI patients requiring dialysis, 12% in Ethiopia(25) and 18% in Nigeria(24) and when admitted to ICU, 28.3%(35). AKI independently, high rifle staging at time of AKI diagnosis, oliguria, hyperbilirubinemia, low levels of bicarbonate, haemorrhagic shock and peuperal sepsis have been shown to correlate significantly with mortality(18,35,36).

In a retrospective study conducted by Huang, C et al in China, 343 cases of pregnant women with AKI were reported amongst 42,173 deliveries, of whom 14 died (4.08%). When live births were considered this number dropped to 8 deaths out of 278 live births, an alarming difference from the country's 2012 maternal mortality rate of 24.5 per 100,000 live births(37). In Canada, mortality rates amongst PrAKI patients was reported at 4.3% vs 0.01% in non-pregnant women (26).

The morbidities faced by these mothers include need for dialysis, admission to intensive care units and with longer stay, increased occurrence of eclampsia and stroke and premature termination of pregnancies(29,38,39) with delivery often being via caesarean section(29,39). Other clinical outcomes of women with PrAKI include increased risk of obstetric haemorrhage, placental abruption and disseminated intravascular coagulation(39).

Maternal PrAKI is associated with poor neonatal outcomes. In 2017, a review of 29 Chinese studies of pregnancies complicated by AKI found a still birth rate of 29.8% versus 6% amongst pregnancies without AKI(38). Data from Africa report

similar peri-natal mortality rates: Malawi 15.4%, Nigeria 34%, Ethiopia 35.7% and South Africa 37.1% with a predominance of premature births. The higher perinatal mortality rates were amongst PrAKI patients requiring dialysis(17,24,25,29).

Majority of patients with renal injury gain full recovery by the time they are discharged from hospital, and others up to 6 weeks thereafter. Rao et el. (2018) quoted proportions of between 40 – 75%(26). In South Africa, Conti-Ramsden et al. (2019) had an overall renal recovery rate of 67% (154 of 230 cases of PrAKI in preeclampsia)(29). Higher rates of recovery were demonstrated across the continent in studies which enrolled general obstetric PrAKI patients: 84.6% in Malawi, 83% in Ethiopia and 76% in Morocco(17,19,25). Similar proportions have been observed in India 89.4%, China and the US, 87% (26,27,38).

Renal recovery was also seen to correlate with severity of PrAKI at presentation. Arrayhani et al. (2013) found a higher RIFLE stage at presentation correlated to unfavourable evolution of PrAKI(19). The same was seen by Conti-Ramsden et al. (2019) who found complete recovery in 90% of patients with stage 1 AKI, 59% in those with stage 2 and 34% in those presenting with stage 3 AKI(29). Conversion to CKD was seen in 4 – 9% of PrAKI patients, and deterioration to End Stage Renal Disease in 1.5 to 2.5% of cases(26,38).

2.6 Diagnosis of PrAKI

The physiological changes in pregnancy result in a drop in the measured serum creatinine (SCr), the effect of which peaks towards the end of the 2nd trimester, mediated by up to 50% increase in glomerular filtration(40). Widely used models to define AKI, such as the Risk, Injury, Failure, Loss and End-stage (RIFLE) published in 2004 by the Acute Dialysis Qualitative Initiative (ADQI) group and the Acute Kidney Injury Network (AKIN) criteria of 2007, are based on the general

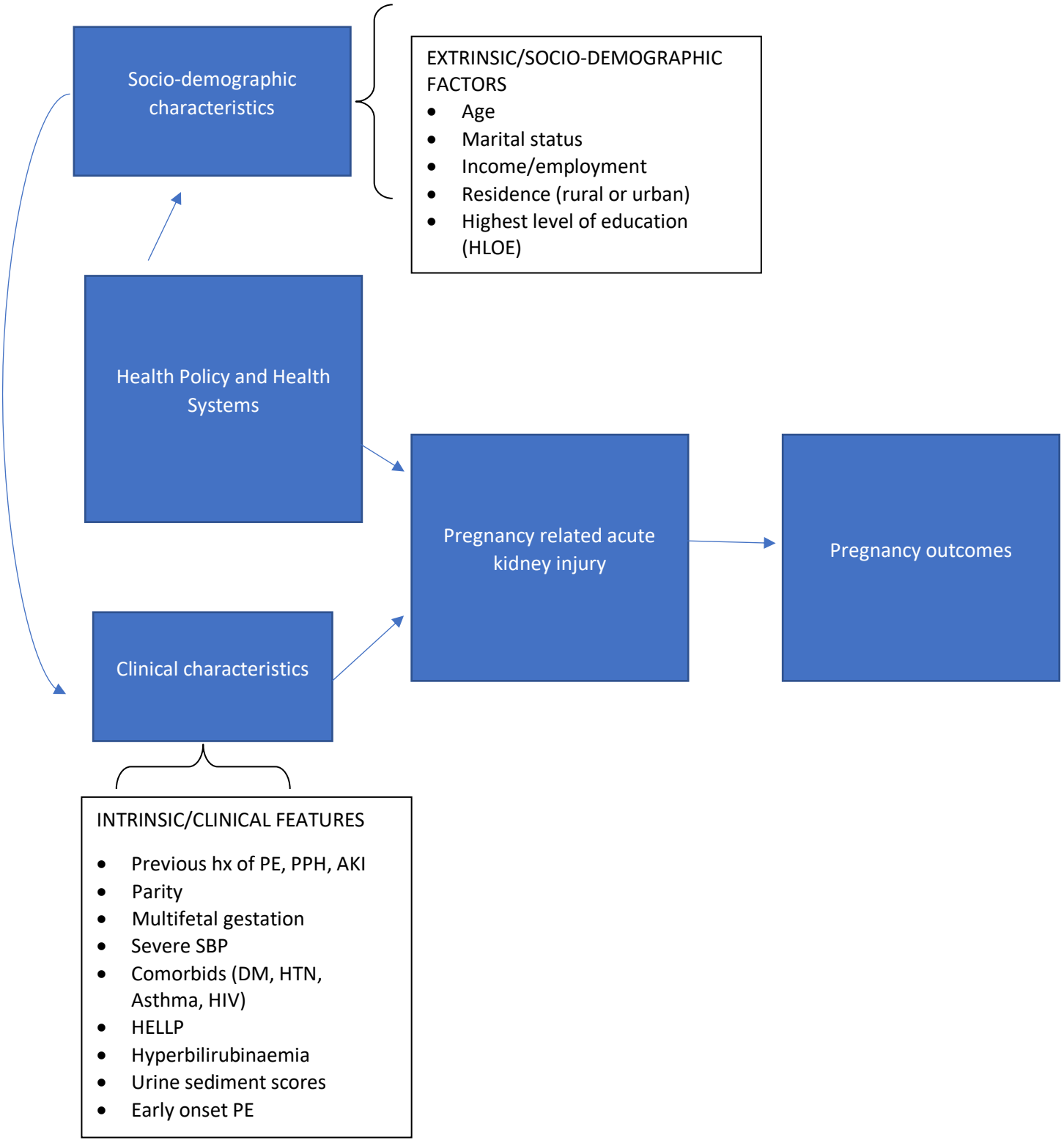
population for whom normal average creatinine values differ compared to the pregnant population(39). This was demonstrated by a meta-analysis comparing 4421 serum creatinine values of pregnant women pooled from 49 studies and matched to those who were non-gravid (SCr values, N= 8659). Wiles et al found a difference in the mean serum creatinine of 84%, 77% and 80% in the pregnancy population as compared to the non-pregnant population at the 1st, 2nd and 3rd trimesters respectively. They recommended a lower threshold of serum creatinine as the upper limit of normal in pregnancy; 76µmol/l in 1st trimester, 72µmol/l in 2nd trimester and 77µmol/l in 3rd trimester(40).

In the absence of the validated models for use in the pregnant population, studies on PrAKI have defaulted to the AKI definition provided by the RIFLE criteria or AKIN criteria, or a combination of both, as given by the KDIGO AKI guideline(4,26,39). For purpose of this study this inherent limitation is accepted as well, and the AKI (PrAKI) definition is based on the KDIGO guideline(4).

2.7 Management of PrAKI

The management of PrAKI in the context of preeclampsia can be considered into general and specific measures, within a multidisciplinary approach: inclusion of the nephrologist and intensivist if needed. General measures include identification of the cause of AKI, eliminating any nephrotoxic agents to prevent further renal injury and fluid resuscitation to counter the intravascular volume depletion, done with caution to prevent pulmonary oedema. Specific measures include timely initiation of renal replacement therapy and delivery of foetus for either obstetric or maternal indications(41).

3.0 Conceptual Framework (Schematic)



AKI, acute kidney injury
ANC, antenatal clinic
DM, diabetes mellitus
HELLP, haemolysis elevated liver enzymes low platelets
HIV, human immunodeficiency virus
HTN, hypertension
PE, pre-eclampsia
PPH, postpartum haemorrhage
SBP, systolic blood pressure

4.0 Study Justification

Hypertensive disorders of pregnancy, specifically preeclampsia, contributes greatly to the burden of PrAKI and associated maternal and perinatal morbidity and mortality. We postulate that adverse outcomes are associated identifiable risk factors that can support early and timely intervention to mitigate severe morbidity and mortality. Data on risk factors for PrAKI is scanty and describes various cohorts of patients either generalised to all obstetric patients, dialysed patients or patients admitted to ICU(25,32,35,36). The cohort selected in this study (patients with preeclampsia admitted to the general maternity wards) bears the greatest burden of PrAKI hence its usefulness. In Kenya, no study has been done that aims to investigate risk factors for PrAKI amongst patients with preeclampsia or determine their pregnancy and renal outcomes.

Currently there are no sophisticated methods in mitigating the effects of PrAKI. As per the 0by25 initiative, and KDIGO guidelines, the primary focus should be on preventing AKI from occurring. Profiling pregnant mothers with known risk factors for PrAKI is an important strategy in achieving the 0by25 initiative, particularly in the resource poor setting.

We propose to evaluate pregnant women presenting with PE associated AKI and define a subset of clinical features or factors that can support identification of 'high risk' women likely to suffer AKI up to its severe form. We anticipate that risk stratification will merit for inclusion of routine creatinine testing as part of their antenatal profile and allow for early intervention, timely referral and optimize maternal and/or foetal outcomes, as seen in the study by Cooke et al(17).

5.0 RESEARCH QUESTION

What are the risk factors for PrAKI amongst women with preeclampsia?

6.0 OBJECTIVES

6.1 Broad objectives

To determine the risk factors, severity and progression of pregnancy related acute kidney injury and the pregnancy (maternal and perinatal) outcomes amongst women with preeclampsia at Kenyatta National Hospital

6.2 Specific objectives

Amongst women with preeclampsia and PrAKI at the Kenyatta National Hospital:

1. Compare predetermined early maternal and perinatal outcomes to those with preeclampsia and no PrAKI
2. Determine severity (by stages) of PrAKI at the time of recruitment and short-term renal outcomes withing 2 weeks.

6.3 Secondary Objective

To determine the differences in urine sediment analysis amongst women with preeclampsia complicated by PrAKI, to compared to those with preeclampsia and no PrAKI

7.0 METHODOLOGY

7.1 Study design

This was a prospective cohort study comparing pregnant women with preeclampsia complicated by AKI to those without AKI for risk factors and the pregnancy outcomes (maternal and perinatal) in the two groups.

7.2 Study setting

The study was conducted at the Kenyatta National Hospital between February 2020 to April of 2020. Participants were enrolled from the Labour Ward as well as Antenatal and Postnatal wards (1A, GFA, GFB) of Kenyatta National Hospital. This is a quaternary level hospital located in the capital city Nairobi, which is a referral centre for lower level hospitals from its environs as well as the county level hospitals from the surrounding regional units of government. Ethical clearance for the study was obtained prior to commencement. The Maternity Unit through its Labour Ward admits patients diagnosed with hypertensive disorders of pregnancy to a High Care Unit within the ward, where they are stabilised and managed until transfer to Ante/post-natal wards. Postpartum mothers more than 72 hours after delivery are also admitted into the acute Gynae ward 1D, however none of these patients were approached or enrolled into the study.

7.3 Study population

Women presenting to the Obstetrics and Acute Gynaecology units indicated above, at KNH were enrolled in to an exposure and non-exposed group if they fit the following eligibility:

Women who were pregnant from 20 weeks gestation, up to 6 weeks postpartum with a diagnosis of preeclampsia with no acute kidney disease (NKD) for the non exposed group and those with preeclampsia and AKI for

the exposed group, as defined in this study in the preceding sections. The threshold for abnormal serum creatinine considered was that used by ISSHP guidelines which is 90µmol/l(1).

7.3.1 Inclusion/ exclusion criteria

Inclusion criteria: Women with a diagnosis of preeclampsia from 20 weeks gestation up to 6 weeks postpartum. Those recruited were further divided into an AKI group (PRAKI +ve) and no kidney disease (NKD) group (PRAKI -ve) depending on the presence or absence of derangements in the renal function. The PrAKI +ve group constituted the exposed group while the PrAKI -ve were the non-exposed group. Patients with preeclampsia and a previous history of AKI, were assigned to PrAKI group.

Exclusion criteria: Women with deranged renal functions from known pre-existing renal disease (CKD) as defined in the preceding sections, or on renal replacement therapy, or previous kidney transplant patients were not eligible for this study.

Women in whom no antenatal health records were available or in whom no laboratory data could be found in their files were also excluded.

7.4 Sample size determination

The sample size for this study was determined from the Fleiss method.

Sample size calculation for finite population.

$$m' = \frac{\left[c_{\alpha/2}\sqrt{(r+1)}\bar{P}\bar{Q} - c_{1\text{-}\beta}\sqrt{rP_1Q_1 + P_2Q_2}\right]^2}{r(P_2 - P_1)^2}$$

$$m = \frac{m'}{4}\left[1 + \sqrt{\{1 + \frac{2(r+1)}{m'r[P_2 - P_1]}\}}\right]^2$$

$$\bar{P} = \frac{(P_1 + rP_2)}{r=1} \qquad \bar{Q} = 100 - \bar{P}$$

$m = n_1$ = Size of sample from population 1 (population 1 = NKD/PRAKI -ve)
n_2 = Size of sample from population 2 (population 2 = AKI/ PRAKI +ve)
P_1 = Proportion of exposure in population 1
P_2 = Proportion of exposure in population 2
α = "significance" = 0.05
β = chance of not detecting a difference = 0.2
1-β = Power = 0.8
r = n_2/n_1 = ratio of exposed to non-exposed participants = 0.25
P = $(P1+rP_2)/(r+1)$
Q = 1- P
n_1 = m
n_2 = rm
From table A.2 in Fleiss, if
1-α = 0.95 then $c_{\alpha/2}$ is 1.960
1-β = 0.8 then $c_{1-\beta}$ is -0.842

P_1 = proportion of exposure (HELLP +ve) in Population 1 (NKD) = 0.05% (21/41,830). This proportion was obtained from Huang et al study which demonstrated that out of 42,173 patients included in their study, 343 patients had AKI and 41,830 had no kidney injury, of whom, 21 patients had HELLP(37).

P_2 = proportion of exposure (HELLP +ve) in Population 2 (AKI) = 9.3% (32/343). This proportion was obtained from the same study which demonstrated that out of 42,173 patients included in their study, 343 patients had AKI of whom, 32 patients had HELLP(37).

$m = n_1$ = Size of sample from population 1 (population 1 = NKD/PRAKI -ve)

n_2 = Size of sample from population 2 (population 2 = AKI/ PRAKI +ve)

r = n_2/n_1 = ratio of exposed to non-exposed. These proportions were taken from a regional study from South Africa which considered PRAKI + cases amongst women with pre-eclampsia. They found that 272 out of 1547 women with preeclampsia had AKI. This

is a proportion of 17.6% (n_2) out of n_1 (100 – 17.6 = 82.4%). Thus r = n_2/n_1 = 17.6:82.4 is approximately 1:4.6 for this study, simplified to 1:4.

$$\bar{P} = \frac{(0.05+[0.25\times9.3])}{0.25+1}$$=1.9 $\bar{Q}$ =100- $\bar{P}$= 98.1

$$m' = \frac{\left[1.96\sqrt{(0.25+1)}1.9\times98.1-(-0.842)\sqrt{0.25(0.05\times99.95)}+9.3\times90.7\right]^2}{0.25(9.3-0.05)^2}$$

$$m = \frac{m'}{4}[1+\sqrt{\{1}+\frac{2(0.25+1)}{m'0.25[9.3-0.05]}\}]^2$$= 150.9

n_1 = non-exposed = 150.9

n_2 = exposed = 0.25×150.9= 37.74 } 188.64

Plus 10% of n_1 = 150.9+ 15.09 = 165.99 » **166**

10% of n_2 = 37.74 + 3.44 = 41.1 » **41**

Final sample size with 10% addition = 166 + 41 = 207

7.5 Sampling procedure and selection of study participants

Non-random, consecutive patient sampling was used. Women who met the inclusion criteria for the study were approached by research assistants enlisted. Later, with the advent of Covid-19 pandemic, patients were recruited by assistants who were part of the healthcare providers allocated to the management of High risk patients on the day of enrolment. Patients were enrolled into study after giving their informed consent.

Eligible patients were identified from examining case files for the diagnosis of preeclampsia according to the operational definitions stipulated. The exposed group were patients who had AKI, 'AKI group' and the non-exposed group were patients with no kidney, 'NKD group' depending on serum creatinine values.

AKI was identified if there was a rise of more than 26.5 µmol/l within 48hrs in 2 consecutive serum creatinine measurements, or there was a difference of greater than 1.5 times between the lowest admission serum creatinine (regarded as the baseline creatinine value) and subsequent measurements.

Where there were serial creatinine values available in the patient's file, the lowest creatinine level pre- or post-recovery was regarded as the baseline creatinine to determine the maximum stage (severity) of AKI reached. Stage 2 AKI patients were identified if there was a difference in peak creatinine value of ≥ 2.0 – 2.9 times from baseline occurring within 7 days. Stage 3 AKI patients were identified if there was a difference in peak creatinine value of ≥ 3 times from baseline occurring withing 7 days or if the peak creatinine value exceeded 353.6 µmol/l.

Urine output readings where documented, were recorded in the data extraction tool, however the data was found to be inconsistent between patients.

Patients considered to have no kidney injury, 'NKD group' if serum creatine readings were within normal range, or those who had only a single creatinine reading during their admission, irrespective of whether the creatinine value was >90µmol/l, so long as it was not above 135µmol/l.

7.6 Method of recruitment

Files from patients admitted in the antenatal wards were screened for eligibility. Eligible patients were approached, informed of the study, and signed on the informed consent form to confirm participation. Parents or legal guardians were approached for consent where the participant was a minor. Participation was highlighted as voluntary and refusal to participate did not affect the care given.

7.7 Data variables

Independent Variables: demographic and select clinical and laboratory characteristics (Table 3).

Dependant variable: AKI versus NKD.

Table 3

Exposure Variables

Demographic Information	Clinical Information	Laboratory Information
Age	Blood pressure reading (SBP>160mmhg)	Hb (on admission) and Antenatal Hb
Parity	Gestational age at delivery	Platelets
Comorbid disease (DM /GDM/Chronic HTN/Cardiac disease)	Urine output (ml/kg/hr OR ml/6hrs)	UEC
Highest level of education (HLOE)	Multifetal gestation	AST, ALT, TB, DB
HIV status	Early onset preeclampsia (EOPE)	Urine sediment analysis
Number of antenatal visits	Eclampsia	Dipstick analysis: protein/ leucocytes / blood
Previous history of PE, GH, PPH, AKI, RRT in pregnancy	HELLP	
	Abruptio placentae	
	PPH	

Demographic information definitions

Age of patient was as recorded in the admission registration printout found at the back of the patient file, which was based on the national identification card.

Parity was defined as the number of deliveries a woman has had above gestational age of 24 weeks.

Comorbid diseases were defined as having a diagnosis of diabetes mellitus, gestational diabetes, chronic hypertension, and cardiac disease in the current pregnancy.

Highest level of education (HLOE) was categorised in this study as primary, secondary, or no formal education as reported by the patient.

HIV status was defined as a positive serology result either recorded in the antenatal booklet or from provider-initiated HIV testing and counselling result done during admission for patients without any documentation in their ANC booklet.

Number of antenatal visits a mother has had during her current pregnancy was derived from the recorded number of visits in the ANC booklet.

Previous history of **preeclampsia (PE)**, **gestational hypertension (GH)**, collectively regarded as previous history of hypertensive disorders of pregnancy, was as reported by the patient in an antecedent pregnancy.

Previous history of **postpartum haemorrhage**, **renal dysfunction (acute kidney injury or renal replacement therapy)** was regarded as a positive occurrence if reported by the patient.

Clinical information definitions

Highest systolic blood pressure was taken as the highest reading recorded within 72 hours of hospital admission, along with its corresponding diastolic blood pressure. Severe blood pressure was taken as SBP ≥ 160mmHg or DBP ≥110mmHg.

Gestation age on admission was calculated from the 1st day of the last normal menstrual period (LNMP). Where mothers were unable to remember the date, the gestation was determined from an obstetric ultrasound estimate.

Multifetal gestation was identified in the case where the mother was gravid with more than one foetus.

Early onset preeclampsia (EOPE) was categorised as proteinuric gestational hypertension occurring after 20 weeks gestation up to 34 weeks.

Eclampsia was defined as the occurrence of generalised tonic clonic convulsion in the context of preeclampsia.

Haemolysis elevated liver enzymes and low platelets (HELLP) was defined the occurrence of haemolysis (raised total bilirubin concentration ≥ 20.5µmol/l), elevated liver enzymes (raised transaminases to twice the upper limit of normal or AST ≥ 70U/l) and low platelets (< 100 × 10^9/l).

Abruptio placentae is the occurrence of premature separation of the placenta occurring prior to delivery.

Postpartum haemorrhage was noted to have occurred when blood loss was more than 500mls within the first 24 hours after delivery.

Laboratory information

Investigations recorded were those done at the Kenyatta National Hospital laboratories, apart from the haemoglobin level done during antenatal clinic attendance.

Haemoglobin level was considered abnormal below 11g/dl as per WHO. The Hb level at the time of antenatal clinic 1st visit, and on admission was recorded.

Platelet count corresponding to the haemoglobin level on admission was recorded and considered as low below 100 × 10^9/l, then moderately if between 50 - 100 × 10^9/l and severe if < 50 × 10^9/l.

Urea, creatinine, and electrolytes (sodium and potassium) investigations were recorded serially where multiple tests were done.

Abnormal creatinine threshold and AKI. Abnormal serum creatinine (SCr) was taken as a reading of ≥ 90µmol/l. A change in serum creatinine was used to diagnose AKI, according to the KDIGO criteria listed earlier. The lowest serum creatinine level reached during the admission was considered as the baseline for the KDIGO criteria. Patients for whom only one serum creatinine was found, were considered as having no acute kidney injury so long as the serum creatine value was not >1.5 times from the abnormal threshold of 90µmol/l (i.e., not greater than 135µmol/l).

Hepatic cytolysis was identified by recording the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values. Abnormal values were taken as > 70U/l.

Haemolysis was identified from the total bilirubin and direct bilirubin values.

Hyper bilirubinaemia in our study was considered significant if ≥ 34.2 µmol/l.

Urine dipstick was used to determine the presence of proteinuria, leucocytes and blood in the urine, and quantified as either 1+, 2+ or 3+.

Urine sediment analysis involved light microscopy of a drop of pellet obtained after centrifuging a urine sample for 5 minutes. Significant findings were the presence or absence of cellular casts, termed as active sediment. The sediment was non active if there were no casts observed. A score was assigned to each sample of urine examined, adopted from Perazella et al (2010) (34).

Definition of early maternal outcomes

These were measured during the patient's admission up to two weeks from enrolment, unless in the event of death or discharge from hospital. These included:

- **Mode of deliver**y: caesarean section or spontaneous vaginal delivery
- **Early renal outcomes:**
  - Need for haemodialysis for AKI or conservative management for AKI.
  - Indications for dialysis included intractable acidaemia, electrolyte derangements (hyperkalaemia), fluid overload, symptomatic hyperuricaemia, and toxins.
  - The renal status at 2 weeks or upon discharge was recorded. A patient was identified as having recovered if the creatinine measurement returned to within 50% of baseline. If the patient had already presented with advanced acute kidney injury, then 50% of baseline was regarded as SCr

of 135µmol/l. Patients were assigned to partial recovery if they did not fit into the full recovery category.

- **Blood pressure at discharge or 2 weeks from enrolment** was recorded. Elevated BP was regarded as SBP > 140mmHg or DBP of > 90mmHg.
- **Alive/ Dead** by the end of follow up.
- **ICU admission/ event requiring ICU admission** as per intensivist review.

Definition of perinatal outcomes: Perinatal outcomes for this study include:

Pre-term vs term delivery and gestation age on delivery. Preterm birth was regarded as birth < 37 weeks (WHO, Nice Guidelines No. 25, (8,44)). Term birth was regarded > 37 weeks up to 41 weeks gestation.

Perinatal death included death in utero (still birth or intrauterine foetal death, IUFD) and early neonatal death which is death of a live born foetus occurring within the first seven days of life. For this study early neonatal death was regarded up to 14 weeks of follow-up.

Admission to new-born unit (NBU) and the length of stay or if discharged to mother immediately after delivery was recorded.

Apgar score at the 1st, 5th and 10th minute from birth was recorded. A poor Apgar score was regarded if below 7 at the 5th minute. (45). (appendix 8)

Birth weight was recorded for both still births and live births. The classification of birth weight was adopted from WHO criteria below(46). For purpose of analysis, the birth weight was grouped as <1500g or ≥ 1500g.

- Low birth weight (LBW) < 2500g
- Very low birth weight (VLBW) < 1500g
- Extremely low birth weight (ELBW) <1000g.

7.8 Data collection procedures

Quantitative data was collected by a data collection form, attached as appendix 3.

Lab investigations were restricted to those done as part of the routine management of the patient requested by the primary doctor in charge. The exception was urine dipstick and sediment analysis. The latter two tests were funded by the study.

Baseline UEC, CBC, LFT, Urinalysis, Coagulation profile, were noted upon enrolment as the first laboratory investigations done from time of admission. Subsequent lab investigations done during the patient's hospital stay were also noted down up till the end of study follow up, discharge or death.

Fresh urine samples were collected for dipstick and urine sediment analysis. Midstream urine sample or indwelling catheter samples were collected to fill a minimum of midway of 50ml specimen bottle and transported to microbiology lab in a bio-hazard bag for immediate microscopy. The minimum required volume for spinning to obtain urine sediment was 15mls. For urine bag samples, the bag was first emptied, then only freshly pooled urine collected for analysis.

The BMI was calculated from the first weight and height recorded in the ANC booklet.

7.9 Materials

Materials used in this study included:

- printed data collection tool kits to extract the raw data.
- Urine dipstick strips: In use at KNH is the Accurate, URS-10T Reagent strips for urinalysis
- Urine specimen bottles

7.10 Training procedures

All, the research assistants were oriented to the data extraction tool. Since they were all health care workers familiar to the hospital, all were competent to collect urine specimen and perform dipstick analysis.

7.11 Quality assurance procedures

The laboratory used employed standard operating procedures as per international and national guidelines. The PI ensured quality control during data collection and entry by double checking all forms at the time of transfer to excel spreadsheet. Forms with missing/ incomplete entries were set aside, and the files of these patients retrieved from the records department to gather all available information.

8.0 ETHICAL CONSIDERATIONS

The study, P434/06/2019, was approved by the KNH-UON Ethics and Research Committee on the 11th October 2019. Participation was voluntary and each patient was requested to sign the informed consent form available in both English and Kiswahili language. Participants could withdraw at any point during the study period. They were also informed of the added urine investigations that were to be paid for by the principle investigator.

9.0 DATA MANAGEMENT

Information from the data collection tool kit (forms) was extracted into excel spreadsheets ahead of analysis by an appointed statistician. The data collection forms were at all times kept in a secure fashion, free from tampering or public view.

Data was summarised and presented by use of tables, charts and graphs, and expressed as frequencies, means, proportions and p-values where appropriate (See appendix).

Data was analysed with the use of Statistical Package for Social Science version 24.0. The demographic data, clinical information and data on pregnancy outcomes were expressed as means, medians and range, and the frequencies (n) expressed as percentages. To determine the risk profile of pregnant women with PE admitted at KNH at high risk for AKI, data was presented as frequencies and proportions. To determine the factors associated with kidney injury in pregnant women with PE, data was analysed with use of Odd Rations (OR) and the associated 95% Confidence Interval (CI) calculated, which formed the univariate analysis and significant variables carried forward to logistic regression analysis, done through STATA software. A p value < 0.05 was considered significant in determining associations.

10.0 STUDY RESULTS DISSEMINATION

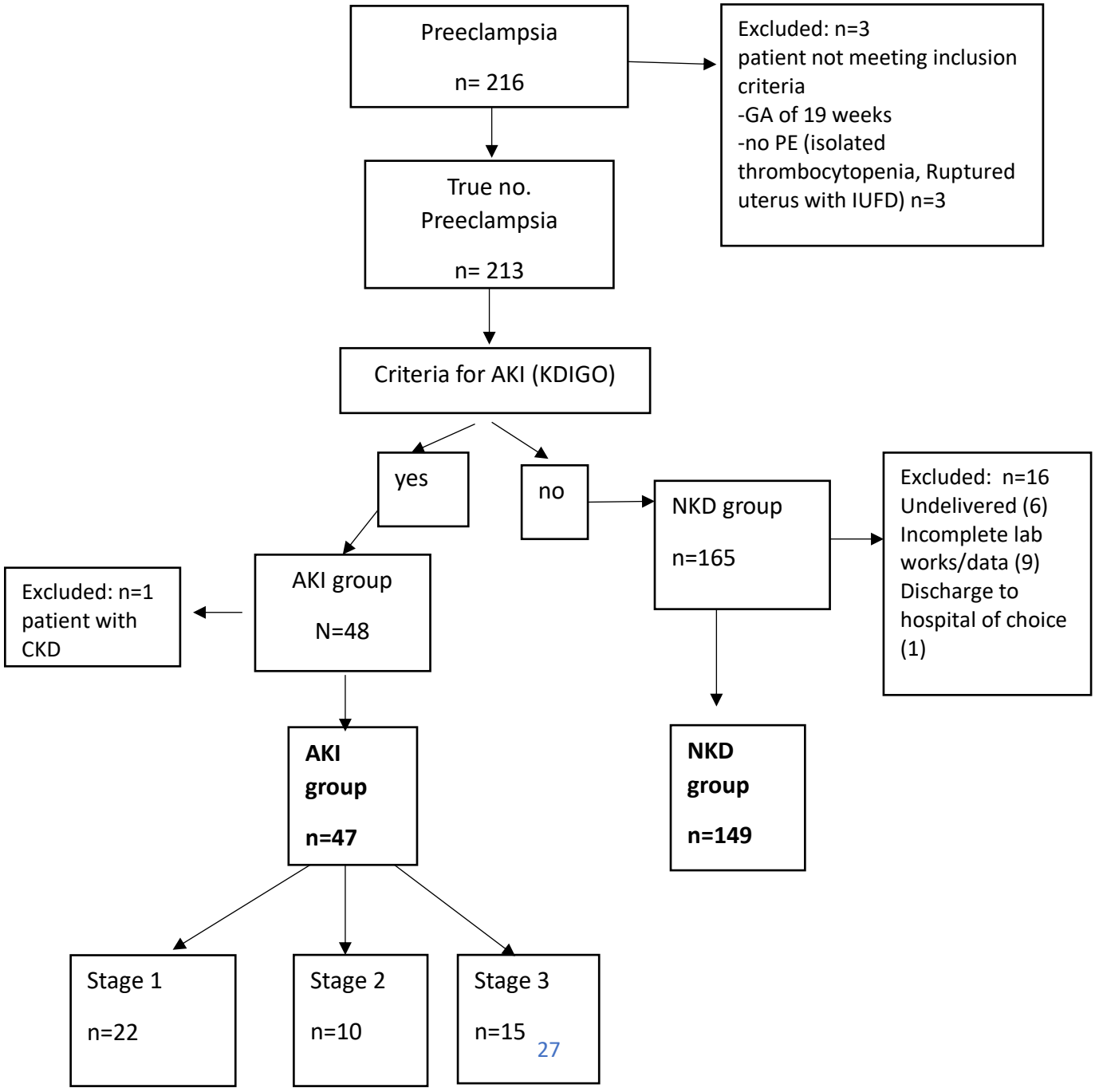
Findings from this study were presented to the Obstetrics and Gynaecology and Kenyatta National Hospital Research departments, thereafter, written up in this dissertation.

11.0 RESULTS

Description of enrolled patients

One hundred and ninety-six, 196, patients were enrolled in this study. Patients with no kidney disease, NKD, were 149 and those with AKI were 47. A total number of 20 patients were excluded. The total number of patients admitted through the labour ward at Kenyatta National Hospital during the study period was 3,057. The study flow is illustrated in figure 2 below.

Figure 2: Study flow chart



Description of enrolled patients

Age distribution of enrolled patients was between 17 to 46 years, with a median age of 31 and mean age of 30 years. Majority of enrolled patients were below 35 years, 74% (145 of 196) of whom 36 patients had PrAKI. There was no significant difference in age between the PrAKI and NKD group.

Majority of the participants (141 of 196) were educated up to secondary and tertiary level respectively, 42.9% (84) and 29.1% (57). Being educated appeared to lower the risk of presenting with PrAKI, as seen by those with primary and tertiary education having significantly lower odds. From the PrAKI group, the severity of AKI was distributed as follows: 11.2% (22) were stage 1, 5.1% (10) with stage 2 and 7.7% (15) with stage 3 disease.

Most patients were multiparous, 68.9% (135) of whom 33 had AKI and 102 had NKD. The mean gestational age was 35 weeks, with a lower mean gestation seen in the PrAKI group (33.4 weeks) compared to the NKD group (35.8 weeks). This difference in means was statistically significant (Table 4).

Risk factors for PrAKI

Women who had PrAKI were likely to have fewer ANC visits (OR 2.6, 95% CI: 1.2-5.5; p=0.013), lower gestation at presentation (under 28 weeks OR 4.2, 95% CI: 1.2 – 14.5; p=0.014), higher urine sediment score (> 4 OR 10.8, 95% CI: 2.1-55.3, and HELLP syndrome (OR 8.5, 95% CI: 4.0-17.9) (Table 4 and 5).

There was no association between advanced maternal age (>35 years), parity, history of hypertension in previous pregnancy, intrapartum complications, ANC booking haemoglobin levels, advanced gestation > 35 weeks. There was one

patient in our cohort with prior history of recovered renal dysfunction and only one patient who was HIV positive, both belonging to the AKI group. (Table 4).

Risk factors by clinical features at the time of hospital admission are shown in table 5. Significant associations were seen in patients with increased urine sediment score, anaemia on admission, early onset preeclampsia (EOPE, OR 1.9, 95% CI: 1.0-3.9) and where preeclampsia was complicated by HELLP syndrome. Patients with a urine sediment score of 1 had lower odds of PrAKI diagnosis although this was not statistically significant (OR 0.5, 95% CI: 0.2-1.0). Other variables subjected to analysis were not found to be associated with the occurrence of PrAKI.

Table 4

Baseline Sociodemographic and Obstetric Characteristics of Study Participants

Characteristic/Risk Factor	PrAKI (47=n_1)	NKD (149=n_2)	P-value
Age			
Median (range)	30.0 (19-43)	31.0 (17-46)	0.958
• *< 20*	3 (6.4)	7 (4.7)	0.695
• 20-34	33 (70.2)	102 (68.5)	0.821
• *35+*	11 (23.4)	40 (26.8)	0.639
Education			
• *None*	2 (4.3)	3 (2.0)	0.395
• ***Primary***	14 (29.8)	36 (24.2)	**0.001**
• *Secondary*	23 (48.9)	61 (40.9)	0.334
• ***Tertiary***	8 (17.0)	49 (32.9)	**<0.001**
Parity			
• *Primigravida*	14 (29.8)	47 (31.5)	0.821
• *Multipara*	33 (70.2)	102 (68.5)	0.821
Gestational Age			
• ***< 28***	6 (12.8)	5 (3.4)	**0.015**
• *28-34*	16 (34.0)	37 (24.8)	0.215
• ***35 +***	25 (53.2)	107 (71.8)	**0.012**
Chronic HTN	10 (21.3)	30 (20.1)	0.865
Term (≥37 weeks)	12 (25.5)	87 (58.4)	**<0.001**
Pre term (<37 weeks)	35 (74.5)	62 (41.6)	**<0.001**
DM/GDM	4 (8.5)	9 (6.0)	0.553
Cardiac Disease	-	1 (0.7)	-
Serostatus (HIV infection)	1 (2.2)	-	-
No. ANC Visit			
• *None*	1 (2.2)	1 (0.7)	0.386
• ***1 – 2***	15 (32.6)	23 (16.0)	**0.013**
• *3 – 4*	21 (45.7)	72 (50.0)	0.662
• *5+*	9 (19.6)	48 (33.3)	0.085
Previous H_X of HDP	7 (14.9)	48 (32.2)	**0.021**
Previous history of PPH	3 (6.4)	2 (1.3)	0.056
H_X of Renal Dysfunction	1(2.1)	-	-

Results presented as n (percentage) or absolute value.
Abbreviations: AKI, acute kidney injury, NKD no kidney disease, OR odds ratio, CI confidence interval, DM diabetes mellitus, GDM gestational diabetes mellitus, HIV human immunodeficiency virus, HDP hypertensive disorder of pregnancy, HTN hypertension, PPH postpartum haemorrhage, H_X history.

Table 5

Association between Clinical, Laboratory Features and occurrence of PrAKI

Characteristic/Risk Factor	PrAKI (47=n_1)	NKD (149=n_2)	OR (95% CI)	P-value
Highest SBP (mmHg)*	170(151,189)	165(154,176)	-	0.285
Multifetal Gestation	2 (4.3)	16 (10.7)	2.3 (0.5-10.2)	0.269
Anaemia Hb (<11g/dl) on ANC Booking	12 (26.7)	48 (33.3)	0.7 (0.3-1.5)	0.402
Hb (on admission)				
• <11 g/dl	24 (51.1)	33 (22.1)	3.7 (1.8-7.3)	**<0.001**
• ≥ 11 g/dl	23 (48.9)	116 (77.9)		
Thrombocytopenia				
• < 50 × 109/l	20 (42.6)	10 (6.7)	10.1 (4.3-24.1)	**<0.001**
• 50-100 × 109/l	8 (17.0)	19 (12.8)	1.4 (0.6-3.4)	0.480
• 101-150 × 109/l	19 (40.4)	120 (80.5)	0.2 (0.1-0.3)	**<0.001**
Urine output				
• < 1000mls /24 hrs**	35 (74.5)	48 (32.2)	6.1 (2.9-12.8)	**<0.001**
Early onset preeclampsia				
• < 28	9 (19.1)	8 (5.4)	4.2 (1.5-11.5)	**0.003**
• < 34 weeks	22 (46.8)	46 (30.9)	1.9 (1.0-3.9)	**0.045**
Eclampsia	7 (14.9)	12 (8.1)	2.0 (0.7-5.4)	0.167
HELLP	26 (55.3)	19 (12.8)	8.5 (4.0-17.9)	**<0.001**
PPH	3 (6.4)	11 (7.4)	0.9 (0.2-3.2)	0.817
Abruptio Placentae	2 (4.3)	-	-	**-**
Urine sediment scores (average)				
• Score 1	11 (23.4)	58 (38.9)	0.5 (0.2-1.0)	0.052
• Score 2	20 (42.6)	56 (37.8)	1.2 (0.6-2.4)	0.542
• Score 3	10 (21.3)	33 (22.1)	1.0 (0.4-2.1)	0.898
• Score 4	6 (12.8)	2 (1.3)	10.8 (2.1-55.3)	**<0.001**
Dipstick analysis:				
-Protein				
• 2+	17 (51.5)	58 (53.2)	0.9 (0.4-2.0)	0.864
• 3+	16 (48.5)	51 (46.8)		
-Leucocytes				
• 2+	4 (33.3)	14 (60.9)	0.3 (0.1-1.4)	0.121
• 3+	8 (66.7)	9 (39.1)		
-Blood				
• 2+	4 (22.2)	12 (31.6)	0.6 (0.2-2.3)	0.469
• 3+	14 (77.8)	26 (68.4)		
Liver Transaminases				
• AST >70U/l	31 (66.0)	29 (19.5)	8.0 (3.8-16.5)	**<0.001**
• ALT >70 U/l	29 (61.7)	28 (18.8)	6.9 (3.4-14.3)	**<0.001**
Hyper-bilirubinaemia: TB ≥ 34.2 µmol/l	18 (38.3)	8 (5.4)	10.9(4.3-27.6)	**<0.001**

Abbreviations: SBP, systolic blood pressure; Hb, haemoglobin; EOPE, early onset preeclampsia; HELLP, haemolysis elevated liver enzymes and low platelets; AST, aspartate transaminase; ALT, alanine transaminase; TB, total bilirubin

*Value expressed as median(Q1,Q3)

There was incomplete data for the BMI category with only 25 entries captured of a total of 196 due to missing documentation in the ANC booklet, particularly in height of patients and was not analysed.

Forty two percent of patients had a urine output of less than 1000mls in the first 24 hrs after enrolment. Placental abruption did not occur in any of the patients in the NKD group, and in only 2 amongst PrAKI group. Eclampsia occurred more frequently amongst patients with PrAKI, 14.9% vs 8.1% in NKD group. The number of pregnancies complicated by PPH was marginally greater in the NKD group (7.4% vs 6.4%). There were no significant associations in the dipstick analysis between groups.

Early maternal outcomes, Table 6

A greater proportion of mothers were delivered via caesarean section 68.9% (135 of 196) and the same pattern was demonstrated in both the PrAKI and NKD groups: 51% of PrAKI patients (24 of 47) were delivered via caesarean section versus 74.5% in the NKD group (111 of 149), however, the odds of SVD was higher in PrAKI group (OR 2.8, 95% CI: 1.4-5.5; p= 0.002). The proportion of patients with PrAKI that underwent dialysis was 21.3% (10 of 47) which constituted 5.1 % of the total sample size. Only 1 patient who was allocated to the NKD group died, for reasons suspected to be related to complications of anaesthesia.

Duration of hospital stay was significantly longer in the PrAKI group (OR 51.2, 95% CI:18.2-144.2; p<0.001). ICU admissions were seen in 7 patients overall, 4 from the PrAKI group and 3 from the NKD group, with higher odds noted in favour of the former, however this association was not significant (OR 2.5, 95% CI: 0.5-11.5; p= 0.233). While the SBP for all patients at time of discharge was on average, 135mmHg, and that of the DBP was 88mmHg, a proportion of patients required anti-

hypertensive treatment upon discharge or end of study follow up: 48.9% (23 of 47) of patients with PrAKI and 32.2% of patients with NKD (48 of 149).

In keeping with PrAKI diagnosis, a greater proportion of these patients had an output of <1000mls per 24hours, 74.5% vs 32.2% and this association was significant (OR 6.1, 95% CI:2.9-12.9; p<0.001).

Perinatal outcomes, Table 6

Significant associations were observed across all perinatal outcomes and their association with PrAKI. Pregnancies complicated by PrAKI had increased odds of preterm birth (OR 4.1, 95% CI: 2.0-8.5; p= <0.001), Stillbirth (OR 6.0, 95% CI: 2.7-13.4; p= <0.001), neonatal mortality (OR 4.8, 95% CI: 1.7-13.4: p=0.001), lower birth weight (<2500g (OR 3.5, 95% CI:1.7-7.4). Consequently, babies born to mothers in PrAKI group had 4.9 times likelihood of New-born Unit (NBU) admission than the NKD group (95% CI, 2.0-12.1: p=<0.001).

Table 6

Early Maternal and Perinatal outcomes in relation to PrAKI and NKD among patients with Preeclampsia

Characteristic/Risk Factor	PrAKI (n_1=47)	NKD (n_2=149)	OR (95% CI)	P-value
Mode of Delivery				
• *SVD*	23 (48.9)	38 (25.5)	2.8 (1.4-5.5)	**0.002**
• *C/S*	24 (51.1)	111 (74.5)		
Need for Dialysis	10 (21.3)	0	0	**0**
Urine Output				
• <1000mls	35 (74.5)	48 (32.2)	6.1 (2.9-12.9)	**<0.001**
Mortality				
• Alive	47 (100.00)	148 (99.3)	-	0.573
• Dead	-	1 (0.7)		
Duration of Admission				
• 1 – 7	15 (31.9)	99 (66.4)	0.2 (0.1-0.5)	**<0.001**
• 8 – 14	11 (23.4)	29 (19.5)	2.3 (0.6-2.8)	0.559
• 14+	21 (44.7)	21 (14.1)	51.2(18.2-144.2)	**<0.001**
ICU admission	3 (6.4)	4 (2.7)	2.5 (0.5-11.5)	0.233
Average BP				
• SBP (DC/14 days)	136(130,143)	130(122,138)	1.4 (0.5-4.7)	**0.005**
• DBP (DC/14days)	92 (81,97)	86 (78,92)	2.0 (0.9-5.1)	**0.044**
BP (DC/14 days, no. of)				
• SBP > 140 mmHg	15 (31.9)	27 (18.1)	2.1 (1.0-4.4)	**0.044**
• DBP > 90mmHg	23 (48.9)	48 (32.2)	2.0 (1.0-3.9)	**0.038**
Perinatal				
Status:				
• Pre-term Birth	35 (74.5)	62 (41.6)	4.1 (2.0 – 8.5)	**<0.001**
• Term	12 (25.5)	87 (58.4)		
Neonatal Outcome				
• Early neonatal death	8 (27.6)	10 (7.4)	4.8 (1.7-13.4)	**0.001**
• Stillbirth (FSB/MSB)	18 (38.3)	14 (9.4)	6.0 (2.7-13.4)	**<0.001**
Birth Weight				
Median	1880 (200-3300)	2470 (400-4240)		
Mean	1,795.7	2,395.6	-	**<0.001**
○ < 2500g	36 (76.6)	72 (48.3)	3.5 (1.7-7.4)	**<0.001**
○ ≥ 2500g	11 (23.4)	77 (51.7)		
5 min Apgar Score < 7	6 (21.4)	4 (3.1)	8.7 (2.3-33.2)	**<0.001**
NBU	21 (72.4)	47 (34.6)	4.9 (2.0-12.1)	**<0.001**
Duration of NBU Admission				
• 1 – 7	9 (42.9)	15 (33.3)	2.1 (0.8-5.1)	0.105
• 8 – 14	4 (19.0)	6 (13.3)	2.2 (0.9-5.5)	0.076
• 14+	8 (38.1)	24 (53.3)	1.1 (0.4-2.5)	0.912

Abbreviations: SVD spontaneous vaginal delivery; C/S caesarean delivery; ICU intensive care unit; D/C discharge; BP blood pressure, END early neonatal death; FSB fresh stillbirth; MSB macerated stillbirth; NBU new-born unit

Renal outcomes, Table 7

Table 7 shows the renal outcomes of the 47 patients diagnosed with AKI in this study. Majority of patients had stage 1 AKI (22), followed by stage 3 AKI (15) and stage 2 AKI (10). The highest creatinine level reached during the time of admission was recorded per patient. The mean serum creatinine was 136.8µmol/l, 225.3µmol/l and 647µmol/l, in stage 1,2 and 3 AKI respectively. Highest recorded serum creatinine was 1138µmol/l. Patients with stage 3 AKI took the longest time to diuresis with an average of 4.9 days compared to the other stages, and this difference was significant, $p<0.001$. Collectively, only 44.7% of patients (21 of 47) had complete recovery at the time of discharge or at the end of study follow up (14 days). A greater proportion of patients who recovered had stage 1 AKI, 86% (19 of 22). 1 out of the 10 patients with stage 2 AKI fully recovered, however the remaining 9 patients were downgraded to stage 1 disease. Of the 15 patients with stage 3 AKI, 1 had fully recovered, 6 and 4 had been downgraded to stage 2 and 1 respectively, and 4 patients remained static by the end of the follow up period. Dialysis was recommended in 10 of the 15 patients with stage 3 AKI and the average number of sessions was 4.2 (approx. 4).

Table 7

Renal outcomes of patients with PrAKI

Characteristic	Stage 1 AKI (n=22)	Stage 2 AKI (n=10)	Stage 3 AKI (n=15)	P-value
Highest Creatinine level				
• *Mean*	136.8	225.3	647.0	**<0.001**
• *Median*	133.0	237.5	620.0	
• *Range*	[91-188]	[104-299]	[371-1,138.0]	
Dialysis				
- No. dialysed	0	0	10 (66.7)	0
- No. dialysis (avg)	0	0	4.2	0
Diuresis (avg days)	1.2	1.1	4.9	**<0.001**
AKI status at DC				
	19	1	1	-
• Stage 1	3	9	4	-
• Stage 2	-	-	6	-
• Stage 3	-	-	4	-
				-

Abbreviations: AKI, acute kidney injury; NKD, no kidney disease; avg, average; DC, discharge

Multivariate logistic regression analysis, Table 8

Logistic regression analysis was done for significant factors identified in the univariate analysis, the outcomes of which are seen in Table 8 overleaf. Aside from the direction of the odds value, the only significant associations with PrAKI were in the occurrence of EOPE below 34 weeks, urine output less than 1000mls per 24hours, severe thrombocytopenia, and birth weight.

Table 8

Multivariate analysis of significant Clinical and Demographic Characteristics for PrAKI

Characteristic/Risk Factor	OR (95% CI)	P-value
Gestation Age: • <28	1.33 (0.63 – 2.79)	0.448
Number ANC visits (1-2)	0.88 (0.65 - 1.20)	0.437
Education Level (Secondary + Tertiary)	1.08 (0.29-4.09)	0.898
Early onset Preeclampsia • < 28, no • < 34 weeks, no	 0.44 (0.01-17.5) 0.06 (0.004 – 0.89)	 0.669 **0.041**
HELLP, YES	0.85 (0.18-3.93)	0.838
Urine Output <1000mls per 24 hours or Oliguria	1.002 (1.001-1.004)	**0.013**
Thrombocytopenia • 50 × 109/l	 0.06 (0.01-0.48)	 **0.008**
Urine sediment scores	0.95 (0.46-1.95)	0.894
Mode of delivery • C/S	 1.93 (0.38-9.81)	 0.425
Blood pressure • SBP • DBP	 0.97 (0.91-1.04) 0.99 (0.93-1.05)	 0.434 0.764
Perinatal mortality • Early neonatal death	 1.65 (0.20-11.7)	 0.605
Birth Weight	1.002 (1.001-1.005)	**0.025**
NBU	0.78 (0.13-4.76)	0.788

Abbreviations: ANC, antenatal clinic; HELLP, haemolysis elevated liver enzymes and low platelets; EOPE, early onset preeclampsia; C/S, caesarean section; SBP, systolic blood pressure; DBP, diastolic blood pressure; NBU, new-born unit; END, early neonatal death

12.0 DISCUSSION

Baseline characteristics for age distribution and parity were comparable to that demonstrated by Conti-Ramsden et al. (2019) with majority of patients in the age bracket of between 20 – 39 years of age and proportion of primiparous patients at 31.1% in our study versus 38.5%. The greater burden of PrAKI in both studies was seen in the age bracket of 30 years and above (53.2% in our setting versus 50.7%). A contrast was seen in the HIV status of our patients; we had 1/196 patients with positive serostatus belonging to the PrAKI group (1/47, 2.1%) against a higher proportion seen in Malawi 1/26 (3.8%) and in South Africa 20/142 (14%) in the AKI

groups. This is reflective of the higher prevalence rates of HIV infection in these two countries(47).

This study aimed to determine the risk factors for PrAKI amongst women with preeclampsia, compare the pregnancy outcomes to those without PrAKI and describe both severity at admission and outcomes of the renal dysfunction at discharge. The main pre-admission risk factors for PrAKI were EOPE. A lower number of antenatal visits could have been confounded to early presentation of preeclampsia hence not significant in multivariate analysis.

Risk factors for PrAKI from the univariate analysis were lower gestational age < 28 weeks, few antenatal visits of between 1-2, higher urine sediment score and HELLP syndrome. These findings are similar to those seen by Nguefack in Cameroon (2018), who found that early onset pre-eclampsia was a risk factor for AKI; Bentata (2012) who found poor antenatal visits and HELLP syndrome to be a risk factor for PrAKI in obstetric patients admitted to ICU and Jonard et al (2014) who found HELLP syndrome in the setting of PPH as a significant risk factor for AKI amongst postpartum patients(30,31,35).

No significant association was found in this study between parameters like previous history of hypertensive disorder of pregnancy (HDP), presence of chronic hypertension, increasing parity and advanced maternal age, to the risk of PrAKI as was found in a large case control study done by Conti-Ramsden et al (2019) in South Africa. They found that the strongest predictor for AKI was previous history of HDP and also the only predictor for severity of AKI (stage 2 and 3 AKI)(29). This can possibly be attributed to the larger sample size of PrAKI patients in the South African study (142 cases to 96 controls).

Intrapartum complications of Eclampsia/HELLP and PPH occurred in similar proportions to the South African study and to global prevalence respectively. The proportions were higher in PrAKI patients which may be attributed to the significantly higher median blood pressures noted compared to NKD patients (table 5 and 6). This might also account for why Abruptio placentae was not reported amongst patients with NKD.

Negative associations to PrAKI in this study that mirrored those found by Conti-Ramsden et al (2019) include, presence of anaemia, thrombocytopenia, and highest proteinuria during admission(29).

In terms of maternal outcomes, while the proportion of caesarean deliveries was higher in the PrAKI group, this association was not significant. This finding mirrored the South African study. All episodes of dialysis reported occurred in the PrAKI group and was similar to previous findings(38,42). While the odds of ICU admission were higher in the PrAKI group, this finding was not significant in contrast to the systematic review by Liu et al. (2017) (38).

There was one mortality documented in this study, however this number was lower than expected as patients enrolled were largely from the labour ward and ante/post natal wards rather than critical care units. There could have been bias in the patients recruited in that patients who could not readily provide consent due to their clinical state were avoided rather than looking for their next of kin, which was provided for in the protocol. 7 patients in our study were transferred to the ICU for further care and those requiring dialysis received appropriate care. This provision of specialised care could also have contributed to the low mortality rates seen. During the data collection months of February to April 2020, there were 7 deaths related to hypertensive disorders of pregnancy which occurred primarily in the ICU and in

theatre (4 out of 7). Two deaths occurred in the labour ward and one in the ante/post natal ward.

Renal outcomes were modest in our study with only 44.7% of patients having complete recovery at the time of discharge or at the end of study follow-up (14 days). This is in contrast to that found by Cooke et al. (2018) who found 84.6% complete recovery at day 7 of admission and by Conti-Ramsden et al. (2019) who found 67% complete recovery at discharge from hospital(17,29). Other reported recovery rates range from 69.4% (cited,(29)), 76% (19), 82.7% (48) and 89.4% (49). This difference may be attributed to a significant proportion of patients who were at stage 3 AKI (32% at admission). Urine sediment analysis done on or during admission showed that a higher sediment score was significant for increasing AKI staging, a finding that was also seen by Perazella et al. (2010)(34). Lower rates of renal recovery in our study may be attribute to the majority of patients falling in stage 2 and 3 categories of AKI. In addition, some patients were discharged prematurely, prior to complete recovery on the basis of falling creatinine levels.

It is not clear why previous history of hypertensive disorders of pregnancy had lower odds of PrAKI, except perhaps due to the limited proportions. In hospital risk factors for PrAKI on univariate analysis were not carried forward in the multivariate analysis apart from severe thrombocytopenia and lower urine output, of which the latter was expected. Delivery via caesarean section was proportionally higher in PrAKI patients, and their mean SBP was higher. Severely elevated blood pressure has been shown to be strongly associated with AKI(28). Perinatal outcomes in mothers with PrAKI were significantly poorer with higher perinatal mortality, lower birth weight, lower Apgar score at 5minutes and greater need for NBU admission. The strongest effect of PrAKI was on birthweight as seen on the multivariate

analysis. Majority of PrAKI patients developed stage 2 and 3 AKI and less than half had full recovery by discharge. The multivariate analysis condensed these findings to EOPE, thrombocytopenia and birthweight as having significant associations to PrAKI.

The relationship of the significant pre-admission risk factors noted above to PrAKI may be explained by the fact that fewer number of ANC visits provides less opportunity for blood pressure surveillance and early recognition of abnormal parameters. The occurrence of EOPE has been shown to be associated with increased incidence of antecedent chronic hypertension and hypertensive disorder of pregnancy, and thus may be the reason why such pregnancies are complicated by PrAKI(30).

In hospital risk factors may be related to the underlying pathophysiological processes of thrombotic microangiopathy (TMA) characteristic of HELLP, which contributes to renal injury. Studies have demonstrated that patients with HELLP have increased incidence of persistent renal dysfunction, need for dialysis and hypertension in the postpartum period. The most common histological lesion in preeclampsia and HELLP patients is acute tubular necrosis, ATN (50). Urine microscopy for such patients is rich in cellular components of tubular epithelial casts, with muddy brown granular casts seen with increasing severity of ATN(34). This is in contrast to the urine microscopy of PE patients without AKI which is often bland and the processes of glomerular endotheliosis and podocyte loss predominates (50). While it has be shown that features of TMA are seen on kidney biopsies in < 15% of patients with HELLP (50), the occurrence of both features of TMA and ATN may be the impetus to developing CKD(42).

The significant higher rates of caesarean delivery seen in PrAKI mothers may be related to the fact that a proportion of them had obstetric indications for operative delivery (gestation below 34 weeks, low estimated foetal weight on ultrasound, evidence of placental blood flow compromise on doppler studies that would preclude vaginal delivery, previous caesarean scars and failed induction).

Perinatal outcomes showed significant higher odds of adverse outcomes across several variables investigated, which was comparable to both regional and international studies(29,38). Cooke et al. (2018) did not find any differences in perinatal outcomes between groups of PrAKI (n=26) versus NKD (n=276), which may be inferred from the reason given for their modest maternal outcomes (no mortality or need for dialysis): the high quality of care provided at the study site (tertiary hospital), use of multidisciplinary approach to care involving both obstetricians and nephrologists, and early pick-up of patients with PrAKI (lower threshold for abnormal serum creatinine, 82µmol/l) (17).

Higher odds of preterm birth and Stillbirth amongst PrAKI patients may be attributed to earlier gestation at presentation and significantly higher median blood pressures compared to NKD group. Consequently, neonates born to PrAKI mothers had higher odds of neonatal mortality, lower birth weights and NBU admission do their prematurity. AKI alone may also be a factor, as seen when adjustments for other variables were done in the study by Conti-Ramsden et al. (2019) (29)

Implications of these findings should see that pregnancy women noted to have higher blood pressures in second trimester, severe thrombocytopenia or HELLP syndrome should be flagged with delivery and stabilisation expedited due to their poorer maternal and perinatal outcomes.

13.0 STUDY STRENGTHS AND LIMITATIONS

This study was ideal as it considered patients with PE, who form the majority of PrAKI patients amongst obstetric population. The study design allowed for investigation of risk factors and has shown that urine sediment analysis may be applicable to an obstetric population.

There are some limitations that exist in this study. There could have been recruitment bias, excluding severely ill patients due to convenience of obtaining consent.

The KDIGO guideline used to diagnose and classify AKI has not been validated for use in the pregnant population. It is however the only available guideline advising diagnosis of AKI.

Another limitation is that since baseline creatinine levels are not routinely done pre-conception, or as part of antenatal care, it was difficult to distinguish patients with pre-existing renal disease from the clinical criteria stipulated in KDIGO CKD guideline (unless reported by the patient) thus may have been included in the study, but in true fact may have had Acute on Chronic Kidney Disease.

Urine samples collected were at times done so post-partum in a number of patients, and thus the finding of haematuria was confounded by lochia. This occurrence was however random between the PrAKI and NKD groups. On microscopy, active urine sediment was the presence of red cell casts, rather than normal looking red cells.

14.0 CONCLUSION

This study demonstrated several factors that are associated with PrAKI amongst patients with preeclampsia that may be used to risk stratify patients at both the clinic level (lower gestation at presentation of preeclampsia) as well as in hospital admission (severe thrombocytopenia). It also demonstrated a greater maternal morbidity with respect to caesarean section and need for dialysis, and perinatal morbidity and mortality.

15.0 RECOMMENDATIONS

This study should be replicated with a larger cohort of patients to see the true relationship of risk factors that seemed to have high odds but were not significant to the occurrence of PrAKI on both univariate and multivariate analysis. Other variables such as those that are known for metabolic syndrome should be included in subsequent studies e.g., BMI, waist circumference and random glucose reading.

Early delivery should be advocated for mothers with preeclampsia and HELLP or high urine sediment scores on admission, before biochemical changes of AKI become apparent.

Mothers with risk factors as identified in this study should be followed up at higher level facilities, and where possible, clinicians to consider routine baseline creatinine testing in the second trimester or the inclusion of point of care urinalysis devices which can provide immediate valuable information on the presence of and degree of active urine sediment(51). Further investigation on the long-term effect of PrAKI is needed.

16.0 SOURCE OF FUNDING

This study was funded through the generous contribution of family members, acknowledged in the first part of this thesis.

17.0 BUDGET

For the 196 patients enrolled into the study, cost per participant was KES 531/- broken down as follows. A breakdown of the budget can be found in the appendix.

Laboratory Investigations (urine sediment analysis, dipstick)	KES 201/-
Printing data collection tool kit	KES 24/-
Total	**KES 225/-**
Total × 196 participants	**KES 44,100**
Statistician	**KES 20,000**
Research assistant (×2 persons)	**KES 20,000**
Lab Technician (×1 person)	**KES 20,000**
Grand Total **For 196 participants = (104,100÷196)**	**KES 104,100** **(KES 531/- per participant)**

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19.0 APPENDICES

Appendix 1: Informed consent

Appendix 2: Consent form

Appendix 3: Data collection form

Appendix 4: Data representation table, example

Appendix 5: Laboratory procedures and references

Appendix 6: Urine sediment scoring system

Appendix 7: Apgar score

Appendix 8: Itemised budget for Mmed research

Appendix 9: Anti -plagiarism check

Appendix 1: Informed consent

Informed consent will be obtained from all participants, prior to enrolling the patient in the study. A detailed explanation regarding the purpose, nature and benefit of the study will be done prior to the consent being signed. The involvement of each participant will be clearly stated, including providing samples for urine, and withdrawal of blood. Participants will also be informed of the follow up visit in 6 weeks after delivery. Involvement is voluntary, and there is no monetary benefit from participation. Each participant will be assured of anonymity: each record will have a unique identification code in place of personal names.

If participants wish to have their partners present at the time of explaining the study, this request will be accommodated.

The consent has been translated into Kiswahili. Either English or Kiswahili language may be used to obtain informed consent.

The consent may be given by patient or partner acting as next of kin. Partners may also sign as witnesses. Non literate individuals may give their consent by use of a thumb print.

Participant Consent Form (English)
Date:

Study Title: "Pregnancy related Acute Kidney Injury Among Women with Preeclampsia at Kenyatta National Hospital: Risk factors, Progression and Pregnancy Outcomes"

Principle Investigator and contact: Dr Nyawira W. Ng'ayu, 0702 965 966

Department of Obstetrics & Gynaecology, University of Nairobi

Investigators Statement: My name is Dr Nyawira Wahome Ng'ayu. I am a post graduate student in the Department of Obstetrics & Gynaecology in the University of Nairobi. I am the principle investigator of a study that aims to look for risk factors that predispose a mother with preeclampsia in developing acute kidney injury. My research will be conducted at Kenyatta National Hospital in the Maternity and Gynaecology wards including Labour Ward, 1A, GFA, GFB, 1D as well as NICU.

Purpose of study: This study will be looking at acute kidney injury in mothers with preeclampsia and their pregnancy outcomes compared to those with preeclampsia alone. Acute kidney injury is a condition where the kidneys abruptly stop functioning as they should (to removing waste products, regulating the body's electrolytes in and making urine). The study also aims to identify the risk factors that would lead to development of kidney injury. If we know the risk factors, we can act early to save these mothers and their babies from bad outcomes.

Procedures: Once you, as the patient or next of kin, or if you are a minor, an appointed guardian agrees to be involved in the study, a questionnaire will be used to collect all the necessary information needed from you as the participant. Laboratory investigations will be done, at various intervals during this admission. To do these investigations both blood and urine samples will be obtained from you (the participant). Involvement in this study will not add any days to your hospital stay, interfere with your management or add any extra costs to your hospital bill. The duration of the study is 2 weeks from enrolment, after which you will continue with routine care and follow up in our antenatal or postnatal clinics.

Risks: There are no anticipated risks.

Benefits: You will benefit from the evaluation of your kidney function and blood pressure, and will be followed up before and after delivery to a maximum of 2 weeks

in the study. If any abnormalities are detected the primary care givers will be notified, and appropriate management instituted.

Voluntariness: Involvement in this study is purely on a voluntary basis. There is no financial reward to be gained. You may withdraw at any point if you wish without any consequence to your care or the care of your child.

Confidentiality: All the information obtained from you the participant will be held in strict confidentiality. Any information that may identify you or your child will not be published or discussed with any unauthorised persons. No specific information regarding you, your child or your family will be released to any person without your written permission. Your research number will be used in place of your names.

Access to health records: you may apply for access to your own records or may authorise a third party such as lawyer, employer or insurance company to do so on your behalf. The principle investigator can be contacted if access to health records is required.

Ethics: This study has been approved by KNH-Uon Ethics Research Committee (ERC). Contacts: P. O. Box 19676 – 00202, Nairobi. Tel (+254-20-) 2726300-9 Ext 44355

Conclusion:

The findings from this study will be shared with the Department of Obstetrics & Gynaecology, University of Nairobi, and to you upon request. The results may be published in scholarly journals.

Appendix 2: Consent form

I ……

after reading the consent explanation form and being explained to by Dr Nyawira Wahome Ngayu (principle investigator) do voluntarily agree to take part in this study on Acute Kidney Injury Among Women With Preeclampsia Admitted To Kenyatta National Hospital, And Their Pregnancy Outcomes.

I am also aware that I can withdraw from this study without losing any benefit or affecting the quality of the management of my medical condition.

Signed/ Thumbprint (patient)…….

Date: …….

Contacts of patient: …….

Physical Address: ……

Guardian/next of kin signature/Thumbprint: …….

Guardian/Next of kin relationship: …….

Witness Name and relationship: …….

Signature/ thumbprint……

Appendix 1 (Kiswahili): Fomu ya Mshiriki wa Dhana

Tarehe:

Kichwa cha uchunguzi: "Pregnancy related Acute Kidney Injury Among Women with Preeclampsia at Kenyatta National Hospital: Risk factors, Progression and Pregnancy Outcomes"

Mtafiti mkuu na nambari ya simu: Dr Nyawira W. Ng'ayu, 0702 965966

Idara ya Afya ya Uzazi, Chuo Kikuu Cha Nairobi.

Jina langu ni Dk Nyawira Wahome Ng'ayu. Mimi ni mwanafunzi katika Idara ya Afya ya Uzazi, Chuo Kikuu ya Nairobi. Mimi ni mfuatiliaji mkuu anaye fanya utafiti ambao una lengo la kuangalia sababu za hatari ambazo hufanya mama na preeclampsia kuendeleza kupata ugonjwa wa figo.

Utafiti wangu itafanyiwa katika Idara ya Afya ya Uzazi, Hospitali ya Taifa ya Kenyatta kwenye kata ya Uzazi ya hospitali ikiwa ni pamoja na kata ya 1A, GFA, GFB, 1D na kata ya Watoto wachanga, NICU.

Kusudi la utafiti: Utafiti huu unalengo la kujua ni mama wangapi walio na preeclampsia walio na ugonjwa wa figo mkali kuhusiana na ujauzito. Kujeruhiwa kwa figo kali ni hali ambayo figo hazifanyi kazi vizuri na hushindwa kuchuja na kutosha taka na maji ya mwili, kutoa mkojo, na kusababisha madhara ya viungo vyote katika mwili. Utafity huu pia unalengo la kutambua sababu za hatari ambazo zinaweza kusababisha ugonjwa wa figo mkali. Ikiwa tunajua sababu za hatari, tunaweza chukua hatua mapema kuwaokoa wamama na watoto wao kutokana na matokeo mabaya yalihusika na ugonjwa wa figo.

Utaratibu: Ikiwa unakubali kushiriki katika utafiti huu au katika kesi ya mdogo, wewe kama mzazi/mlezi wa mdogo kukubali kwamba anapaswa kushiriki katika utafiti dodoso itatumika kukusanya taarifa kutoka kwa kila mshiriki. Uchunguzi wa maabara utafanyika kwa vipindi tofauti wakati wa kulazwa hospitali. Kufanya uchunguzi huu, wewe kama mshiriki utapeana sampuli ya mkojo na kuchukuliwa sampuli ya damu. Kuhusika na utafiti huu hakutaongeza siku yoyote kwa kukaa hospitali, wala kuingilia kati ya matibabu yako au koungezeka kwa garama ya hospitali. Wewe kama mshiriki utafwatiliwa kwa wiki mbili. Uchunguzi wa maabara utafanyika wakati huu pia.

Hatari: Hakutakuwa na hatari yoyote.

Faida: Utafaidika kwa ufafanuzi ya hali ya figo na kupima shinikizo la damu, na kufwatiliwa baada ya kujifungua. Ikiwa shida lolote itakapogunduliwa daktari wa msingi atafahamishwa na matibabu yaliyofaa kuanzishwa.

Kujitolea: Utafitu huu utakuwa kikamilifu kwa hiari. Hakutakuwa na tuzo za kifedha kwako kwa kushirika katika utafiti. Mshiriki anaweza kujiondoa kwenya utafiti wakati wowote bila kuathiri wewe au huduma ya mtoto wako kwa njia yoyote.

Usiri: Taarifa zote zilizopatikana kutoka kwako mshiriki utafanyika kwa siri kali. Maelezo yoyote ambayo yanaweza kutambua wewe au mtoto wako haita chapishwa au kuzungumzwa na watu wowote ambao halali. Hakuna habari maalum kuhusu wewe, mtoto wako au familia yako itatolewakwa mtu yeyote bila idhini yako iliyoandikwa. Nambari yako ya utafiti itatumika badala ya majina yako.

Upatikanaji wa recodi za afya: Unaweza kuomba upatikanaji wa recodi zako au unaweza kuidhinisha vyama vya tatu kama vile wanasheria, waajiri au kampuni za bima za afya kufanya hivyo kwa niabayako. Mpelelezi mkuu anaweza kuwasiliana kama upatikanaji wa recodi za afya unahitajika.

Maadili: Utafiti huu imeruhusiwa kufanya na KNH-Uon Ethics Research Committee (ERC). Mawasiliano: P. O. Box 19676 – 00202, Nairobi. Tel (+254-20-) 2726300-9 Ext 44355

Hitimisho:

Matokeo ya utafiti huu yatashirikiwa na Idara ya Afya ya Uzazi, Chuo Kikuu ya Nairobi na kwa mshiriki juu ya ombi. Pia inaweza kuchapishwa katika majarida ya wasomi.

Appendix 2 (Kiswahili): Fomu ya Idhini

Mimi ……

baada ya kusoma fomu ya ufafanuzi wa ridhaa na kuelezewa na Dk Nyawira Wahome Ngayu (mchunguzi mkuu) kwahiari ninakubali kushiriki katika utafiti huu uliyo na lengo la kuangalia sababu za hatari ambazo hufanya mama na preeclampsia kuendeleza kupata ugonjwa wa figo. na baadaye matokeo yao na kwa watoto wao, walio lazwa katika kata za Idara ya Afya ya Uzazi katika Hospitali ya Taifa ya Kenyatta.

Ninajua pia ya kwamba ninaweza kujiondoa kwenye utafiti huu bila kupoteza faida yoyote au ubora wa matibabu ya shida yangu

Ishara/ Kuchapisha kidole (mgonjwa): ……..

Tarehe: ……

Mawasiliano ya mgonjwa: ……

Makao/ Anwani ya kimwili: ……

Msimamizi/Jamaa ya pili, ishara/kuchapisha kidole: …….

Uhusiano ya msimamizi/jamaa ya pili: ……..

Shahidi, jina na uhusiano: …….

Ishara/kuchapishakidole: ……

Appendix 3: Data collection form

Section 1: Identification

Study Identification number	
Hospital Number	

Section 2: Demographics

a) Age (yrs.):

b) Gravid / Parity:

c) Gestational age – on recruitment [ ] delivery: [ ]

d) Multifetal gestation: yes [ ] no [ ]

e) Comorbidities (yes/no/mode of diagnosis):

	yes/no	Mode of diagnosis
Chronic HTN		
GDM		
Cardiac disease		

f) Highest level of education:

g) Gestational age at ANC booking:

Number of antenatal visits prior to admission:

Booking Hb:

Booking HIV status:

h) Previous history (yes/no):

	Yes/no
Preeclampsia	
Gestational hypertension	
AKI	
PPH	
RRT	

Section 3: Clinical Information

	DAY 0	DAY 3	DAY 7	DAY 10	DAY14	D/C
BP (highest)						
Urine output (ml/kg/hr OR ml/3hrs OR ml/24hrs)						
BMI		-	-	-	-	-
PPH						
HELLP						
Abruption Placentae						
EOPE (PE at GA < 28wks)		-	-	-	-	-
ECLAMPSIA						

Section 4: Laboratory/Radiological Information

	DAY 0	DAY 3	DAY 7	DAY 10	DAY 14	D/C
Hb						
Platelets						
PT/INR		-	-	-	-	-
Dipstick analysis: protein Bilirubin, blood						
UEC						
LFT(ALT/AST/TB/DB)						

Section 5: Maternal Outcomes

Mode of delivery (c/s or svd)	
Duration of hospital stay (days)	
Time to diuresis	
BP at discharge.	
Alive / Dead	
ICU admission / event requiring ICU admission	
Dialysis	

1. (yes/no) 2. number of dialysis sessions	

Section 6: Foetal Outcomes

Term/ Preterm and age at delivery	
Birth Weight	
Foetal deaths (still birth-fsb/msb)	
Neonatal Mortality (death 0 -28 days)	
Apgar score for live births	
NICU admission 1. (yes/no) 2. Duration of admission	

Appendix 4: Data representation tables (Dummy Tables).

Table 1: Demographic data of women with acute kidney injury (AKI) and no kidney disease (NKD).

Characteristic/ Risk factor	**All patients n=x**	**AKI n=y**	**NKD n=x-y**
Age			
Parity			
Gestational Age			
HLOE			

Table 2: Severity of AKI (by stages) at start and end of recruitment

KDIGO staging	N=x number of total patients	
	Admission	Discharge/death
Stage 1 (>26.5 µmol/l or 0.3mg/dl increase in Creatinine within 48 hours OR 1.5-1.9 times baseline within 7days OR urine output <0.5ml/kg for > 6 hours)		
Stage 2 (2.0-2.9 times baseline within 7 days OR urine output <0.5ml/kg for 12 hours)		
Stage 3 (≥3 times serum creatinine from baseline within 7 days or serum creatinine of ≥353.6 µmol/l or 4.0mg/dl with an acute increase of > 44.2 µmol/l or 0.5mg/dl OR initiation of renal replacement therapy (RRT) OR <0.3ml/kg/hour of urine for 24hours OR anuria for > 12hours OR in patients < 18years a decrease in eGFR to <35ml/min per 1.73m^2)		

Table 3: Pre admission Risk Factors (demographic and clinical data) for patients with acute kidney (AKI) and no injury kidney disease (NKD).

Characteristic/ Risk factor	All patients n=x	AKI n=y	NKD n=x-y	P value
Age <20 20-34 >35				
Parity -Primiparous -Multiparous				
Gestational Age at delivery ≤27 28-34 ≥34				
Multifetal gestation				
Chronic HTN				
Anaemia <11 g/dl <8 g/dl				
DM/GDM				
Cardiac disease				
HIV infection				
Number of antenatal visits < 4 ≥ 4				
Previous history of hypertension disorder of pregnancy in past pregnancy (preeclampsia + gestational htn)				
Previous history of PPH in past pregnancy				
Previous history of Renal dysfunction in past pregnancy (AKI+ RRT)				

KEY: AKI- acute kidney injury, NKD – no kidney disease, HTN – hypertension, GDM- gestational diabetes mellitus, DM – diabetes mellitus

Table 4: Risk Factors by post admission clinical features for patients with acute kidney (AKI) and no injury kidney disease (NKD)

Characteristic/ Risk factor	All patients n=x	AKI n=y	NKD n=x-y	P value
Highest SBP (mmHg)				
Hb (on admission) ≥ 11g/dl 8-10.5g/dl < 8g/dl				
Thrombocytopenia < 100 × 10^9 /l				
BMI ≥ 30 kg/m^2				
Urine output < 1000mls per 24 hrs (0.59ml/kg/hr for 70kg individual)				
EOPE ≤ 27 wks 28 -34 > 34 wks				
Eclampsia				
HELLP				
PPH				
Abruptio Placentae				
Urine sediment scores (average) -Score 1 -Score 2 -Score 3				
Dipstick analysis: -Protein - 2+ - 3+ -Leucocytes - 2+ - 3+ -Blood - 2+ - 3+				
Liver Transaminases - AST >70U/l - ALT >70 U/l				
Hyperbilirubinaemia: TB ≥ 34.2 µmol/l				

KEY: AKI- acute kidney injury, NKD – no kidney disease, BMI – body mass index, EOPE- early onset preeclampsia, Hb- Haemoglobin, HELLP – haemolysis, elevated liver enzymes and low platelets, AST – aspartate transaminases ALT- alanine aminotransferase, TB – total bilirubin, DB – direct bilirubin

Table 5: Maternal Pregnancy outcomes

Characteristic	**All patients n=x**	**AKI n=y**	**NKD n=x-y**	**P value**
Mode of delivery: SVD				
Mode of delivery: Caesarean Section				
Mortality				
Duration of Hospital Admission				
ICU admission (recommended or admitted)				
Duration of ICU admission				
BP (at end of follow-up or discharge) -Average SBP -Average DBP				
Need for anti-hypertensive treatment (at end of follow-up or discharge) -No. of patients with SBP > 140mmHg -No. of patients with DBP > 90mmHg				

KEY: AKI- acute kidney injury, NKD – no kidney disease, SVD – spontaneous vertex delivery, ICU- intensive care unit, BP – blood pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure, No.- number

Table 6: Renal outcomes

Characteristic	Stage 1 AKI	Stage 2 AKI	Stage 3 AKI	OR	P-value
Highest Creatinine level (avg/ median, range)					
Dialysis -no. receiving dialysis - avg number of dialysis sessions					
Diuresis (average time in days)					
No. of those down staged at time of discharge					

Table 7: Perinatal Pregnancy outcomes

Characteristic	All patients n=x	AKI n=y	NKD n=x-y	P value
Preterm birth <27 wks 28-34 wks >34 wks				
Term >37wks birth				
Intrauterine foetal death (IUFD)				
Early neonatal death (END)				
Fresh Still Birth (FSB)				
Apgar Score (at 5 minutes, average)				
Birth Weight ≥ 2500g <2500g				
NBU admission				
Duration of NBU admission				
Discharge to mother after delivery				

Appendix 5: Laboratory procedures and references

Laboratory procedures were done as per as per set SOPs for each unit.

Lab reference values adopted from the Kenyatta National Hospital Haematology, Biochemistry and Obstetrics and Gynaecology Laboratories in conformity to the respective international accepted unit of measurement and reference value.

Appendix 6: Urine sediment scoring system(34)

RTE cells (per HPF)	Granular Casts (per LPF)		
	0 (0 Points)	1 to 5 (1 Point)	≥6 (2 Points)
0 (0 points)	0	1	2
1 to 5 (1 point)	1	2	3
≥6 (2 points)	2	3	4

Values denote total points awarded.

Appendix 7: Apgar Score(45)

APGAR SCORE

Gestational Age _____ weeks

SIGN	0	1	2	1 minute	5 minute	10 minute	15 minute	20 minute
COLOR	Blue or Pale	Acrocyanotic	Completely Pink					
HEART RATE	Absent	<100 minute	>100 minute					
REFLEX IRRITABILITY	No Response	Grimace	Cry or Active Withdrawal					
MUSCLE TONE	Limp	Some Flexion	Active Motion					
RESPIRATION	Absent	Weak Cry; Hypoventilation	Good, crying					
			TOTAL					

Comments:

Resuscitation

Minutes	1	5	10	15	20
Oxygen					
PPV/NCPAP					
ETT					
Chest Compressions					
Epinephrine					

FIGURE 1

Expanded Apgar score form. Record the score in the appropriate place at specific time intervals. The additional resuscitative measures (if appropriate) are recorded at the same time that the score is reported using a check mark in the appropriate box. Use the comment box to list other factors including maternal medications and/or the response to resuscitation between the recorded times of scoring. PPV/NCPAP indicates positive-pressure ventilation/nasal continuous positive airway pressure; ETT, endotracheal tube.

Appendix 8: Itemised Budget for Mmed research

Topic: Acute Kidney Injury Among Women with Preeclampsia at Kenyatta National Hospital: Risk Factors, Progression and Maternal Foetal Outcomes

Minimum Sample Size: 189. Total participants enrolled were 196.

Investigations to be conducted:

Test	Number of repeats/patients	Total number of tests (196 patients	Details of cost	Total Cost KES
Dipstick	1	196	100 strips/ container @ Kes 100	200/-
Urine Sediment Analysis	1	196	@ KES 200 per analysis	39,200/-
Printing		196	@KES 24 per participant	4,704/-
Statistician			KES 20,000/-	20,000/-
Research assistant	2		@KES 10,000 per assistant	20,000/-
Lab technician	1		KES 20,0000/-	20,000/-
Total				**KES 104,104/-**
Grand Total				**KES 104,104/-**

Appendix 9: Anti-plagiarism check

Done by use of Turnitin software. Outcome: 7%