FACTORS AND CLINICAL FEATURES ASSOCIATED WITH DEVELOPMENT OF HELLP SYNDROME AMONG PATIENTS WITH PREECLAMPSIA WITH SEVERE FEATURES AT THE KENYATTA NATIONAL HOSPITAL

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DECLARATION

I declare that the work presented herein is my original work, has not been presented for the award of any degree at any other institution or university, and has been supervised by senior members of the Department of Obstetrics and Gynecology, University of Nairobi, School of Health Sciences, Faculty of Medicine, Kenyatta National Hospital, Nairobi, Kenya.

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CERTIFICATE OF SUPERVISION

This is to certify that this dissertation by Dr EvelyneAwuor Okello was researched upon under our supervision and that this book is submitted with our approval as university supervisors.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACOG: American College of Obstetrics and Gynecology

ANC: Ante-Natal clinic

ARF: Acute Renal Failure

BP: Blood Pressure

CS: Caesarian Section

DIC: Disseminated Intravascular Coagulopathy

FSB: Fresh Still Birth

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets

HTN: Hypertension

ICU: Intensive Care Unit

KNH: Kenyatta National Hospital

MGSO4: Magnesium Sulphate

MSB: Macerated Still Birth

ND: Neonatal Death

PE: Preeclampsia

WHO: World Health Organization

ABSTRACT

Background

HELLP syndrome is considered a complication of preeclampsia with severe features; which is one of the hypertensive diseases in pregnancy. It is still not well understood why some patients with severe preeclampsia develop HELLP while others do not. HELLP syndrome contributes to considerable morbidity and mortality in both the mother and the fetus.Understanding the factors and clinical features associated with the development of HELLP syndrome among patients with severe preeclampsia would help clinicians have a high index of suspicion and thus identify patients at risk early and manage them appropriately to prevent adverse maternal and perinatal outcomes associated with the condition.

Study Objectives: Among patients withpreeclampsia with severe feature, to determine the socio-demographic, obstetric and clinico-pathological characteristics of patients with and without HELLP syndrome; and the association between preeclampsia and the development of HELLP syndrome.

Methodology: This study adopted a case control study design. Data was collected from 316 records of patients with a diagnosis of PE with severe features, who attended maternity and delivery services at the Kenyatta National Hospital (KNH) for the period January 2014 to December 2016. The cases comprised of 97 records of patients with a diagnosis of PE with severe features and HELLP syndrome. The controls comprised of 219 records of patients with PE with severe features without HELLP syndrome. Data on socio demographic, obstetric and clinical factors was extracted from the patient records and an association between a diagnosis of severe preeclampsia and development of HELLP syndrome established. Socio demographic data was presented in form of tables. Multivariate analysis was conducted using SPSS version 21 to establish any association between the factors and clinical features and the development of HELLP syndrome. The study findings were presented in tabular form. A level of significance of 0.05 was taken as significant statistically.

Results: A total of 316 records of patients with PE with severe features were reviewed. Cases comprised 97 records of patients with HELLP syndrome while controls comprised 219 records of patients without HELLP syndrome. The mean age of patients with HELLP syndrome was 29.5 years. There was a statistically significant association between having a history of epigastric pain and development of HELLP syndrome. Elevated levels of creatinine of more than 110 micromoles/ml also increased the risk of developing HELLP syndrome 4 fold.There was no association between education level, marital status and age and the development of HELLP syndrome. Similarly, parity, gestational age and a previous history of PE or HELLPdid not increase the risk of developing HELLP syndrome. A history of headache, blurring of vision, level of blood pressure and proteinuria did not increase the risk of developing HELLP syndrome as well.

Conclusion: Significant risk factors for developing HELLP syndrome were a positive history of epigastric pain and elevated creatinine levels > 110 micromoles/litre.

CHAPTER ONE: INTRODUCTION

1.1: BACKGROUND OF STUDY

HELLP was previously referred to as edema-proteinuria-hypertension gestosis type B in the early 20th century and was later renamed in 1982 by Louis Weinstein, after its characteristics. It's an abbreviation of the three main features: Hemolysis, elevated liver enzymes and low platelet count (1).

The spectrum of hypertensive disease in pregnancy includes preeclampsia – eclampsia, gestational hypertension, chronic hypertension and preeclampsia superimposed on chronic hypertension (2).

Hypertensive disorders of pregnancy affect about 10 -15% of all pregnancies and cause about 30% of all maternal deaths and 20% of neonatal and fetal deaths (3). Most of the maternal deaths in Latin America have been associated with hypertensive diseases (4).

A study done in KNH in 2006 by Gicheru K found that severe hypertensive disorders occurred in 1.14% of deliveries (5). Another study in the same setting in 2004 by Karanja J. gave the prevalence of hypertensive disorders in pregnancy as 6.5%; 55% of which were preeclampsia,37% eclampsia, 2.7% transient hypertension, 2.7 % chronic hypertension and 2.1% preeclampsia superimposed on chronic hypertension (6)

Preeclampsia is one of the five direct causes of maternal mortality. WHO documents that in 2014, the major direct causes of maternal deaths were obstetric hemorrhage (27%), preeclampsia/eclampsia (14%), infections (11%), unsafe abortions (8%), and obstructed labor (9%) (4). A study done by Musa et al at the KNH in 2017 found that hypertensive disease (eclampsia and preeclampsia) was the leading cause of maternal mortality (7)

A study done by Prabhanjan et al in Ethiopia at the Dilla University Hospital found an incidence rate of preeclampsia of 2.23% (8). Another study done by Solwayo et al in Zimbabwe in 2017 found an incidence rate of severe preeclampsia / eclampsia of 1.3% (9).

The American College of Obstetrics and Gynecology (ACOG) defines hypertensive disorders of pregnancy by at least two blood pressure (BP) readings of 140/90 mmHg or more taken at least 6 hours apart occurring after 20 weeks of gestation (10).

Severe preeclampsia (PE) is defined by presence of one or more of the following using the ACOG criteria: systolic BP > 160 mm Hg or diastolic BP > 110 mm Hg on two occasions 4 hours or more apart while the patient is at rest, thrombocytopenia (platelet count < 100,000 per microliter), impaired liver function as indicated by abnormally elevated blood levels of liver enzymes (to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both, progressive renal insufficiency (serum creatinine > 1.1 mg/dl or a doubling of the serum creatinine in the absence of other renal disease), new onset cerebral or visual disturbances and pulmonary edema (10).

HELLPis an acronym that stands for Hemolysis, Elevated Liver Enzymes and Low platelets.

There are two classification systems for HELLP syndrome. The first one is called Tennessee classification and is based on the number of abnormalities that are present. This is further subdivided into two: partial HELLP with one or two abnormalities and full HELLP which features all the three abnormalities.

Alternatively, HELLP syndrome can be classified on the basis of platelet count nadir (Mississippi classification) as: Class I, < 50,000 per mm^3 (50×10^9 per L); Class II, 50,000 to

<100,000 per mm^3 (50 to 100 × 10^9 per L); Class III, 100,000 - 150,000 per mm^3 (100 to 150 × 10^9 per L).

HELLP syndrome poses a significant risk of morbidity and mortality for both the fetus and the mother, more so in developing countries that are plagued by poor infrastructure, paucity of health information, low levels of education and a poorly resourced health system.

1.2: LITERATURE REVIEW

This section will explore the related literature on the burden, risk factors, pathophysiology, clinical features, management and outcomes of patients with HELLP syndrome.

1.2.1: Burden of HELLP syndrome

A study by Haram and associates showed that HELLP syndrome occurs in 0.5-0.9% of all pregnancies and in 10-20% of patients with severe preeclampsia (11). In comparison, preeclampsia occurs in 2.5 – 7% of all pregnancies (12)(13) .

Another study by Vigil De Gracia and associates in Latin America found HELLP presents in 12% of patients with severe preeclampsia (14). A review done by Sibai and coworkers revealed considerable differences concerning the incidence of the syndrome. The reported incidence ranging from 2-12% reflects the difference in diagnostic criteria used to describe this syndrome (15). In Kenya, a study done by Ng'ayu et al in KNH reported an incidence of 2.8% among patients with hypertensive disease in pregnancy (16).

1.2.2: Risk factors for development of HELLP syndrome

A review by Dusse and associates and another one by Haram et al showed that HELLP syndrome typically occurs between week 27 of gestation and delivery, or immediately postpartum in 15%-30% of cases (17)(18) In a study by Sibai et al, 70% of patients with HELLP syndrome were diagnosed antepartum and 30% post-delivery (15).

When preeclampsia is not present, diagnosis of the syndrome is often delayed. In addition, the mean age of pregnant women with HELLP syndrome is usually higher than in women with severe preeclampsia without HELLP syndrome (19)(20). Sibai's study showed that the incidence of HELLP syndrome is significantly higher in whites and women of European descent and that cv HELLP occurs in older maternal age of 25 years and above (15).

Most white women with HELLP syndrome are multiparous (21). There are no published studies done on black women to compare with.

1.2.3: Pathophysiology of HELLP syndrome

The exact pathophysiology of HELLP syndrome is not clearly understood. There is a debate on whether HELLP syndrome should be considered a severe form of preeclampsia or a separate disease entity. It is not clear why some patients with severe preeclampsia develop HELLP syndrome and others do not. It is argued that these patients have more endothelial injury with greater activation of the coagulation system.

Paternoster et al showed evidence of a compensated DIC in patients with HELLP syndrome compared to normotensive control patients with preeclampsia without HELLP. They found statistically significant differences in plasma fibronectin and D dimer levels and decreases in antithrombin 3 in the patients with HELLP syndrome compared to those without HELLP. Their findings suggest more endothelial damage and consumption of coagulation inhibitors with activation of fibrinolysis in patients with HELLP syndrome than in those with preeclampsia without HELLP syndrome (22).

HELLP is a syndrome characterized by thrombocytopenia, hemolytic anemia, and liver dysfunction believed to result from micro vascular endothelial activation and cell injury.

It is thought that, because HELLP is a variant of preeclampsia, the pathophysiology stems from a common source. In preeclampsia, defective placental vascular remodeling during weeks 16-22 of pregnancy with the second wave of trophoblastic invasion into the decidua results in inadequate placental perfusion. The hypoxic placenta then releases various placental factors such as soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), which then binds vascular endothelial growth factor (VEGF) and placental growth factor (PGF), causing endothelial cell and placental dysfunction by preventing them from binding endothelial cell receptors (23). The result is hypertension, proteinuria, and increased platelet activation and aggregation.

In addition, activation of the coagulation cascade causes consumption of platelets due to adhesion onto a damaged and activated endothelium, in addition to microangiopathic hemolysis caused by shearing of erythrocytes as they traverse through capillaries laden with platelet-fibrin deposits. Multiorgan micro vascular injury and hepatic necrosis causing liver dysfunction contribute to the development of HELLP syndrome (24).

A study by Weiner et al in 2016 reported that although severe preeclampsia and HELLP syndrome have similar placental histopathologic findings, HELLP syndrome was associated with higher rates of placental maternal vascular supply lesions and small-for-gestational-age neonates (25).

Nelson J and his associates proposed that there could be acute maternal immune rejection

due to immunocompetent maternal cells coming into contact with a genetically distinct fetus, altering the maternal-fetal immune balance and causing endothelial dysfunction, platelet activation and aggregation, and arterial hypertension (25).

In addition, dysfunction in the complement system via excessive activation or defective regulation for a given amount of endothelial injury has been proposed to cause damage to hepatic vessels in HELLP, as was demonstrated by Fang C and his colleagues (25).

The histologic pattern of injury in the liver in preeclampsia is fibrin deposition in the periportal sinusoids and hemorrhage into the space of Disse, resulting in hepatocellular necrosis. Blood can dissect through portal connective tissue and collect to form subcapsular liver hematoma. Aarnoudse et al studied needle biopsies of the liver in patients with HELLP syndrome and noted periportal lesions consisting of neutrophilic infiltrates, necrosis of hepatocytes and fibrin microthrombi, and fibrin deposits in the sinusoids. They concluded that the basic histopathologic changes in the liver are identical to those previously described for preeclampsia (26).

Barton et al studied patients who had HELLP syndrome and were delivered by caesarian section, and underwent needle biopsy of the liver under direct visualization. They found fibrin deposition, periportal hemorrhage, and fatty infiltration in 11 patients with HELLP syndrome. There was no correlation between the severity of the histologic findings and the clinical and laboratory findings (27).

1.2.4: Clinical features of HELLP syndrome

History

Patients with HELLP syndrome usually present before term (1).A complete review of systems may reveal malaise, nausea, vomiting, weight gain, and various other nonspecific symptoms (28).

A study by Sibai et al showed that nausea, vomiting, and epigastric and right upper quadrant pain were reported in 30-90% of patients, while headache was present in 33-68%, visual changes in 10-20%, and jaundice in 5% (28).

Women with partial HELLP have fewer symptoms and subsequently develop fewer complications than those with the complete form (28).

Physical examination

Patients with HELLP syndrome show various signs, many of which are synonymous with preeclampsia. A complete physical examination may show signs of dehydration and weakness.

A study by Barton et al showed proteinuria to be present in 86-100% of patients and hypertension in 80%, 55-67% of patients presented with nondependent edema while right upper quadrant tenderness was found in 65-90% of patients, and jaundice in 5% of patients (21). However, a study by Sibai et al showed that hypertension or proteinuria was absent or slight (1).

1.2.5: Laboratory features

The laboratory criteria used for diagnosis of HELLP syndrome varies among institutions, and comparison of patients is complicated by the lack of uniform definitions of the three components of the disorder.

Hemolysis is the most difficult feature to detect, yet probably the most specific, but is frequently not defined. Tests for liver enzymes include several different methods for enzyme analysis with varied reference ranges. Thrombocytopenia has been classically defined as platelet count <150,000/ml.

Hemolysis

Hemolysis is the most difficult feature to detect, yet probably the most specific. Markers for hemolysis include elevated indirect bilirubin and low haptoglobin levels. Morphologic features on peripheral blood smear indicative of hemolysis include schistocytosis (fragmented cells), polychromasia (implying reticulocytosis), anisocytosis, and poikilocytosis. Increased reticulocyte counts reflect the compensatory release of immature red cells into peripheral blood.

Weinstein described hemolysis based on the presence of schistocytes and/or Burr cells on peripheral smear. Destruction of red blood cells by hemolysis causes increased serum lactate dehydrogenase (LDH) levels and decreased hemoglobin concentrations (29)(30). Liberated hemoglobin is converted to unconjugated bilirubin in the spleen or may be bound by haptoglobin in plasma. The hemoglobin – haptoglobin complex is cleared rapidly by the liver, leading to undetectable or low haptoglobin levels in the blood. Low haptoglobin concentration (1g/L - <0.4g/L) can be used to diagnose hemolysis (31)(32).

Sibai recommended that increased bilirubin and LDH be required for the diagnosis of hemolysis, but these lack specificity (1).

The most sensitive and objective marker of hemolysis in the HELLP syndrome is a reduced serum haptoglobin level (29).

In a prospective study measuring laboratory markers of hemolysis in HELLP Syndrome in 1992, Wilke and associates measured laboratory variables of hemolysis in 25 patients with HELLP syndrome. They found reduced haptoglobin in all the 25 patients.

Elevated bilirubin and plasma hemoglobin levels were observed in 5 patients while an abnormal peripheral smear was found in only 11 patients. They suggested that haptoglobin is a sensitive marker for early detection of moderate hemolysis in HELLP syndrome (29).

Elevated Liver enzymes

Hepatic injury in HELLP syndrome is manifest by elevation in AST and ALT. LDH elevation also occurs in liver injury. Sibai defined elevated liver enzymes by an AST value of > 70 U/L (15)(1). Other authors have used elevation of AST and ALT to two standard deviations above the mean to define the elevated liver enzyme component of HELLP syndrome (22).

Low Platelets

In a study by Weinstein, 18 of 29 patients had thrombocytopenia, defined as a platelet count of <100,000/ml on admission, and all 29 patients had a nadir platelet count of <100,000/ml (33). Other authors have also defined thrombocytopenia as a platelet count of <100,000/ml (15)(22).

1.2.6: Maternal and perinatal outcomes of HELLP syndrome

HELLP syndrome poses significant risks for both maternal and perinatal morbidity and mortality. A review by Martin et al showed that patients with class I HELLP syndrome are at higher risk for maternal morbidity and mortality than patients with class 2 or 3 HELLP syndrome (34).

Maternal outcomes

Maternal complications of HELLP syndrome are: Hematologic: DIC, bleeding, hematoma; Cardiac: Cardiac arrest, myocardial ischemia; Pulmonary: Pulmonary edema, respiratory failure, pulmonary embolism, adult respiratory distress syndrome (ARDS); CNS: Hemorrhage/stroke, cerebral edema, central venous thrombosis, seizures, retinal detachment; Renal: Acute renal failure, chronic renal failure; Hepatic: Hepatic hematoma with possible rupture, ascites, nephrogenic diabetes insipidus; infection and even death.

Maternal mortality in HELLP syndrome ranges from 0 – 4 % (33)(15)(35).

In the series by Sibai et al, there were five maternal deaths: one from pulmonary embolism, one from ruptured liver hematoma, and three from diffuse hypoxic encephalopathy (15). Weinstein et

al reported one maternal death (33). Adverse maternal outcomes have been shown to be more in patients with preeclampsia complicated by HELLP syndrome than in those with preeclampsia without HELLP. A study by Yildimir et al in Turkey in 2011 compared perinatal and maternal outcomes in patients with severe preeclampsia, eclampsia and HELLP and found the rate of adverse maternal outcomes at 3.4%, 11.4% and 13.8% respectively (36).

Caesarian section is a common mode of delivery in patients with HELLP syndrome, with rates ranging from 42 – 98% (33)(15). Wound hematoma and infection commonly occurs after cesarean section in these patients. There is also the risk of DIC in HELLP patients. A study by Audibert et al described a risk of 15 % of patients, half of whom had placental abruptions (20). The series by Sibai et al reported acute renal failure in 8% of the patients and eclampsia in 5% of the patients. Other complications reported in this series include pleural effusion (6%), severe ascites (8%), pulmonary edema (6%) and subcapsular liver hematoma (1%) (15).

Perinatal outcomes

Perinatal complications of HELLP syndrome may include: Prematurity, Intrauterine growth restriction and thrombocytopenia with intraventricular hemorrhage or even death. These may require admission to NICU.

Perinatal mortality ranges from 5 – 20% (33)(37). In a study of perinatal outcomes between patients with severe preeclampsia with and without HELLP syndrome in 2005, Gul et al described overall fetal mortality of 10.3% versus 4.6% and perinatal mortality of 16.8% versus 8% respectively with statistically significant differences (38). Ascoglu et al found an overall perinatal mortality of 20.5% in the HELLP group compared to 9.9% in the patients with severe preeclampsia without HELLP syndrome (39).

Magann et al at the University of Mississippi showed that ultimate neonatal survival was related to gestational age and birth weight (40).

Weinstein et al reported hematologic abnormalities in neonates born to mothers with HELLP syndrome. These included leukopenia, thrombocytopenia and abnormal peripheral smears. He noted that 92% of these neonates had abnormal peripheral blood smears with burr cells (33).

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In a study of neonatal outcomes in pregnancies after preterm delivery of HELLP syndrome by Aslan et al in 2004, there were significant differences in the incidence of intra uterine growth restriction, intra uterine fetal death, abruption placenta and fetal distress (41).

1.2.7: Management of HELLP syndrome

The treatment of HELLP syndrome aims at reducing morbidity and preventing complications. Early recognition of HELLP syndrome begins with a thorough history, vital signs, and physical examination. Principles of management include seizure prophylaxis, hypertension control and repletion of blood products, as indicated and general stabilization of patient condition.

Seizure Prophylaxis

Women with HELLP syndrome can develop eclampsia as a complication. Di et al found an incidence of eclampsia with HELLP syndrome of 22% (42). Several studies have revealed that MgSO4 is the drug of choice for treating and preventing eclamptic seizures which may occur in patients with HELLP syndrome. In a Cochrane review by Lelia et al, they found that MGS04 reduces the relative risk of maternal death, of further seizures, and of serious maternal morbidity, (43) while a study by Ecaterina et al reported that women receiving MgSO4 had a 58% less

chance of developing eclampsia. In their study in 2005, Naz et al found that MgSO4 was an effective anticonvulsant both for control and prophylaxis of seizures in eclampsia and improved maternal and fetal outcome (44). MGS04 also gives physiologic advantages to the fetus by increasing uterine blood flow.

Patients on MGSO4 therapy should be evaluated to ensure that deep tendon reflexes are present, respirations are at least 12 breaths per min, and urine output is at least 100 mL during the preceding 4 hours.

MGS04 therapy is continued for 12-24 hours following delivery and may be stopped when hypertension resolves and the patient has shown adequate diuresis.

A Cochrane review published in 2010 concluded that although strong evidence supports the use of MGSO4 for treating and preventing eclamptic seizures, there is not enough research to show the best dose and route for administering it.

MgSO4 4 g IV over 5 min, plus 10 g deep IM divided in both buttocks and mixed with 1 mL 2% lidocaine and a maintenance dose of 5 g IM q4h, starting 4 hours later unless patellar reflexes are absent, respiratory depression occurs, or urine output is < 100 mL in the prior 4 hours.

Intravenous MgSO4 is given until 24 hours after delivery, and stopped if the maternal condition is improved. The IV dosage is a 6-g loading dose over 20 minutes with a 2-g per hour maintenance dose.

Treatment of Hypertension

Hypertension is managed similarly to hypertension in preeclampsia. The BP goal is to keep the systolic at 160mmHg or less and the diastolic at 105mmHg or less. Labetalol and hydralazine are the recommended drugs to treat a hypertensive crisis (45)(46). Caution needs to be exercised when administering intravenous anti-hypertensives to prevent a sudden drop in pressures that

could compromise placental perfusion and lead to fetal demise. Methyldopa, nifedipine and labetalol have been used safely in pregnancy (47).

Corticosteroid Therapy

Corticosteroid therapy in patients with HELLP syndrome remains controversial. Steroids have been theorized to alter the degree of intravascular endothelial injury and prevent further hepatocyte death and platelet activation (48). A prospective study done by Kedra et al at The University of Mississippi Medical Center concluded that an important mechanism of dexamethasone administration is to blunt the release of both antiangiogenic and inflammatory factors suggested to play a role in the pathophysiology of HELLP syndrome (49). While evidence of maternal improvement is limited, some studies such as the one by Sibai and associates have demonstrated improved laboratory findings, including improved platelet counts, liver function, blood pressure, and urine output with the use of high-dose dexamethasone (28).

A retrospective analytical study by Jr. Martin JN et al in 1997 showed that patients who received dexamethasone therapy for postpartum onset HELLP syndrome experienced a shorter disease course, faster recovery, less morbidity and less need for other interventions compared -with those who did not receive dexamethasone (50). Steroids are also believed to improve fetal morbidity by reducing the incidence of respiratory distress syndrome and intraventricular hemorrhage. A meta-analysis by Mao et al showed that corticosteroid administration to HELLP patients improves platelet counts and the serum levels of LDH and ALT and reduces hospital stay and bloodtransfusion rate (51). A Cochrane review published in 2010 concluded that there is insufficient evidence of benefits regarding substantive clinical outcomes to support the routine use of steroids for the management of patients with HELLP syndrome (52).

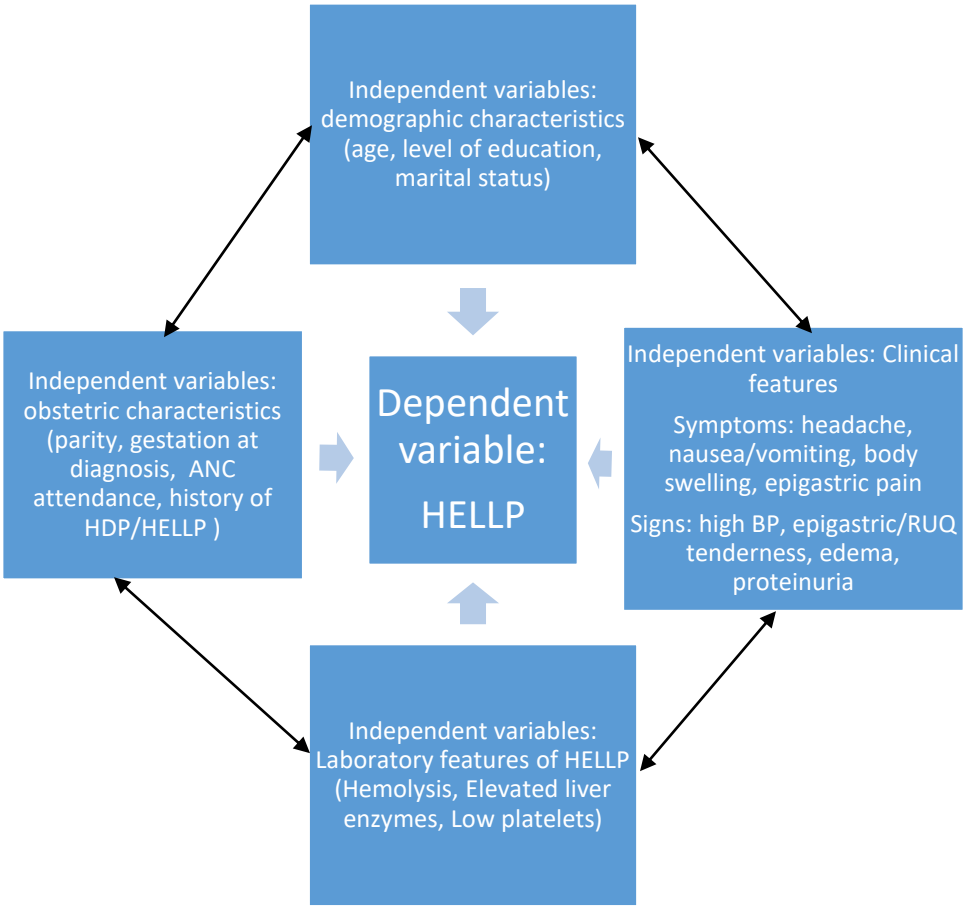
Delivery

Delivery is the ultimate treatment for patients with HELLP syndrome. Delivery (either vaginal or cesarean section) is indicated if HELLP syndrome occurs close to 34 weeks' gestation, in the setting of fetal lung maturity, or upon evidence of significant maternal or fetal distress before 34 weeks' gestation (48).

Treatment of Hepatic Hematoma

Hepatic hematoma usually manifests as a subcapsular hematoma. Barton et al recommended close observation in patients with unruptured hematomas so long as the maternal condition is stable (53). Rupture would necessitate urgent resuscitation and laparotomy to drain the hematoma.

1.3: CONCEPTUAL FRAMEWORK



Conceptual Framework Narrative

Several risk factors have been shown to contribute to the development of HELLP syndrome among patients with PE with severe features. These include advanced maternal age, being of the Caucasian race, having a previous history of HELLP syndrome, chronic hypertension or PE and multiparity. This study, therefore, sought to establish the risk factors that contribute to the development of HELLP syndrome among patients with PE in our setting. The study looked at the

socio-demographic characteristics, obstetric characteristics, clinical features and laboratory parameters of patients with PE with severe features with and without HELLP syndrome.

1.4: JUSTIFICATION OF THE STUDY

The HELLP syndrome carries severe risks for both maternal and perinatal morbidity and mortality. Understanding the factors that contribute to its development would enable physicians taking care of patients with severe PE to have a high index of suspicion and therefore be more vigilant in their treatment and follow up. This will help prevent and timely manage some of the adverse maternal and perinatal outcomes.

Although there are some studies on this topic globally, there is paucity of information on the risk factors that predispose some patients with severe PE to develop HELLP syndrome; especially in our setting and in Africa in general. The study by Sibai et al that was done in Latin America showed that multiparity, being of advanced age and being of the Caucasian race were important risk factors that predisposed patients with severe PE to developing HELLP syndrome (15). Ng'ayu et al found the prevalence of HELLP syndrome to be 2.8% among patients with HDP, and there was a trend to have more hemolysis among patients with higher parity(16)**.** His was however done more than 20 years ago. Since then, a lot has changed; women are now delaying childbirth to advanced ages in pursuit of career development, and families are opting to have fewer children than before. Given the changing scenario, it would be important to know the factors and clinical features that are associated with the development of HELLP syndrome among patients with severe preeclampsia in our setting today.

Also, more studies are needed on this important yet poorly understood disease entity. Information from this study will, therefore, provide a further understanding of HELLP syndrome

which will give guidance during formation of guidelines of management of patients with severe preeclampsia and HELLP syndrome.

CHAPTER TWO: RESEARCH DEFINITION

2.1: PURPOSE OF THE STUDY

To determine the factors and clinical features associated with the development of HELLP syndrome among patients with severe preeclampsia in Kenyatta National Hospital

2.2: RESEARCH QUESTION

What are the factors and clinical features associated with the development of HELLP syndrome among patients with PE with severe features in Kenyatta National Hospital?

2.3: NULL HYPOTHESIS

There is no difference in the factors and clinical features between patients with PE with severe features with HELLP syndrome and those without HELLP syndrome in Kenyatta National Hospital.

2.4: STUDY OBJECTIVES

Broad Objective

To determine the factors and clinical features associated with the development of HELLP syndrome among patients with severe preeclampsia at the Kenyatta National Hospital.

Specific Objectives

Among patients with PE with severefeatures in KNH, to determine the:

1. Socio-demographic and obstetric characteristics of patients with and those without HELLP syndrome.
2. Clinico-pathological presentation of patients with and those without HELLP syndrome.
3. Association between PE with severe features and the development of HELLP syndrome.

CHAPTER THREE: RESEARCH DESIGN AND METHODOLOGY

3.1: STUDY DESIGN

The study adopted a case control study design. Cases were patients with PE with severe features and HELLP syndrome while controls were those without HELLP syndrome. Cases to controls ratio was 1:2.

3.2: STUDY SITE AND SETTING

This study was conducted at the Reproductive Health department of the Kenyatta National Hospital. KNH is located in Nairobi County and is the largest teaching and referral hospital in Kenya. It has a bed capacity of 1800 beds and is located 2 kilometres southwest of the Nairobi Central Business District. This hospital has a busy reproductive health department that conducts 20 – 50 deliveries per day. The labour ward is the initial place where most patients with PE are admitted. Others are first seen in the antenatal clinics then get admitted to labour ward. After stabilization, some patients are immediately delivered while others are managed conservatively in the antenatal wards.

3.3: STUDY POPULATION

The study participants were selected from the records of patients who attended maternity services at the KNH and had a diagnosis of PE with severe features, at or after admission, from January 2014 to December 2016 as per the ACOG diagnostic criteria (10):

a. Systolic BP > 160 mm Hg or diastolic BP > 110 mm Hg on two occasions 4 hours or more apart while the patient is at rest
b. Thrombocytopenia (platelet count < 100,000 per microliter)

c. Impaired liver function as indicated by abnormally elevated blood levels of liver enzymes (to twice the normal concentration)
d. Severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
e. Progressive renal insufficiency (serum creatinine > 1.1 mg/dl or a doubling of the serum creatinine in the absence of other renal disease)
f. New onset cerebral or visual disturbances
g. Pulmonary edema

From the population of patients with a diagnosis of PE with severe features, a review of the files was conducted to establish those patients with laboratory features of HELLP syndrome; random sampling was done to achieve a sample size of 97. Subsequently, 214 records of patients without laboratory features of HELLP syndrome were randomly sampled to form the control group.Information on the exposure variables of interest was then extracted from the records.

3.3.1: Inclusion Criteria

1. Records of patients with a clear diagnosis of PE with severe features as per the ACOG criteria.
2. Records of patients with laboratory results: complete blood count, renal function tests and liver function tests.
3. For cases, patients with at least one laboratory feature of HELLP syndrome.
4. For controls, patients with no laboratory feature of HELLP syndrome.

3.3.2: Exclusion Criteria

1. Records of patients with PE with severe features with no laboratory results.
2. Records of patients with other forms of hypertensive diseases other than preeclampsia.

3. Records of patients with known liver, renal or hematologic disease.

3.4: SAMPLE SIZE DETERMINATION

Sample size was calculated using the difference in proportions - Fleiss JL formula (Statcalcepi-info™) as outlined below. The following assumptions were considered during the calculation (Sibai et al):

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

n = sample size per arm

Study Assumptions

r = ratio of controls to cases, 2:1 in this case

P_1= proportion of patients with HELLP syndrome who had elevated creatinine levels (50%)

P_2=proportion of patients with HELLP syndrome who did not have elevated creatinine levels (50%)

Ṕ =measure of variability, taken as 50+50/2

Z_{β}=Value corresponding to the power of the study, in this case 80% = 0.84

Zα = Value corresponding to the normal standard deviate at 95% C.I in this case = 1.96, with 0.05 level of significance

Applying this in the Statcalcepi info software gives a value of 95 for the cases and 214 for the controls totaling to 309 as shown below:

Un matched Case - Control Study - Sample size

Calculation

					Fleiss
Two sided Confidence Interval	95%		**Kesley**	**Fleiss**	**w/CC**
Power	80%	**Exposed**	89	87	**95**
Ratio of Controls to cases	2.25	**Unexposed**	201	196	**214**
Percent of Controls Exposed	50%		290	283	**309**
Odds Ratio	2.1				

Sample size for the study was 309 patients with PE with severe features; 95 cases (patients with HELLP syndrome) and 214 controls (patients without HELLP syndrome).

3.4.1: Study Participant Selection and recruitment

All files of patients diagnosed with severe preeclampsia in KNH from January 2014 to December 2016 that fulfill the inclusion criteria formedthe study target population. 316 records of patients with severe preeclampsia were selected to be included into the study. Using random sampling procedure, 97 records of patients with HELLP syndrome and 219 records of patients with PE without HELLP syndrome were isolated to be included in the study.

The records were then reviewed for completeness of data on the critical exposure and outcome variables. All the records were retrieved from the Records department at the KNH after seeking a written authorization from the Chief Records officer. Data extraction was done by the principal investigator and two other research assistants and entered into a structured data extraction tool.

3.5: DATA COLLECTION

Data was obtained from the Records Department at the KNH. Relevant data was extracted from sampled files; information extracted included socio-demographic and obstetric characteristics, clinical features, and laboratory parameters. Extracted information was filled into a structured questionnaire data collection tool. Data collected was then entered into the Statistical Package of Social Sciences (SPSS) software version 21 and the computer waspassword protected.

3.5.1: Data Quality Assurance Procedures

Pre-test of the study instrument was carried out to be able to structure and modify the grammar used so as to avoid bias, misinterpretations, ambiguity and improve content validity. The principal researcher sought the assistance of two research assistants with experience in data collection and training to help in data collection. The Principal researcher then checked the filled questionnaires for completeness and accuracy on a daily basis. The questionnaires did not bear the patients names to conceal identity. All the data collection tools were kept in lockable cabinets and the soft copy password protected. This was only accessible to the principal investigator.

3.6: DATA MANAGEMENT

Data was extracted from the hospital files and filled into the study questionnaire (appendix No 1). Data was then checked for completeness and correctness before being entered into the SPSS version 23 software database with in-built consistency and validation checks. The data was then cleaned and stored on a password-protected computer and backed up on a dedicated USB drive. Any hardcopy records carried for analysis were stored under lock and key. The data was only be accessible to the principal investigator and the research statistician.

3.7: DATA ANALYSIS

Data was coded, processed and cleaned off any inconsistencies and outliers. SPSS version 21 was used to analyze quantitative data from the questionnaires. Descriptive statistics including frequencies, percentages, mean, standard deviation, median and mode were used to describe patients' age and parity. Binary and chi-square tests were used to analyze the distribution of socio-demographic and clinical factors among patients with and without HELLP syndrome. Odds ratios were estimated using logistic regression to measure the association between the factors and clinical features associated with the development of HELLP syndrome. A p value of 0.05 was taken to be statistically significant.

3.8: ETHICAL CONSIDERATIONS

Ethical approval was sought from the University of Nairobi-Kenyatta National Hospital Ethics and Research Committee (P646/09/2018). Upon approval, consent was sought from the Head of clinical services, KNH and the head of Records department. Information collected was treated with utmost confidentiality and no patient identifiers were included in the questionnaire or any presentations arising from the study.

3.9: STUDY RESULTS DISSEMINATION PLAN

The study results were presented to the Department of Obstetrics and Gynecology, University of Nairobi. Presentations will also be done in other fora such as conferences and seminars.Attempts will be made to publish the study in a reputable journal by December 2019.

3.10: STUDY CLOSURE PLAN AND PROCEDURE

Study closure was done once data collection was complete, the data de-identified and there were no identifying links or codes to the de-identified data.

3.11: STUDY LIMITATIONS

1. Missing information from files / incomplete records and variables. This was minimized by ensuring strict inclusion criteria of files that contain specific parameters as outlined in the inclusion/exclusion criteria selection.
2. Missing files. This was mitigated by having a three year study period so as to increase the number of files available for sampling. Any missing record was replaced with another consecutive one that fit the inclusion criteria.

3.12: STUDY TIME FRAME

ACTIVITY	May 2018	June 2018	July 2018	Aug 2018	Sept 2018	Oct 2018	Nov 2018	Dec 2018
Proposal preparation and presentation								
Ethical review and approval								
Data Collection								
Final dissertation preparation and results presentation								

BUDGET

Item	**Amount (Kshs)**

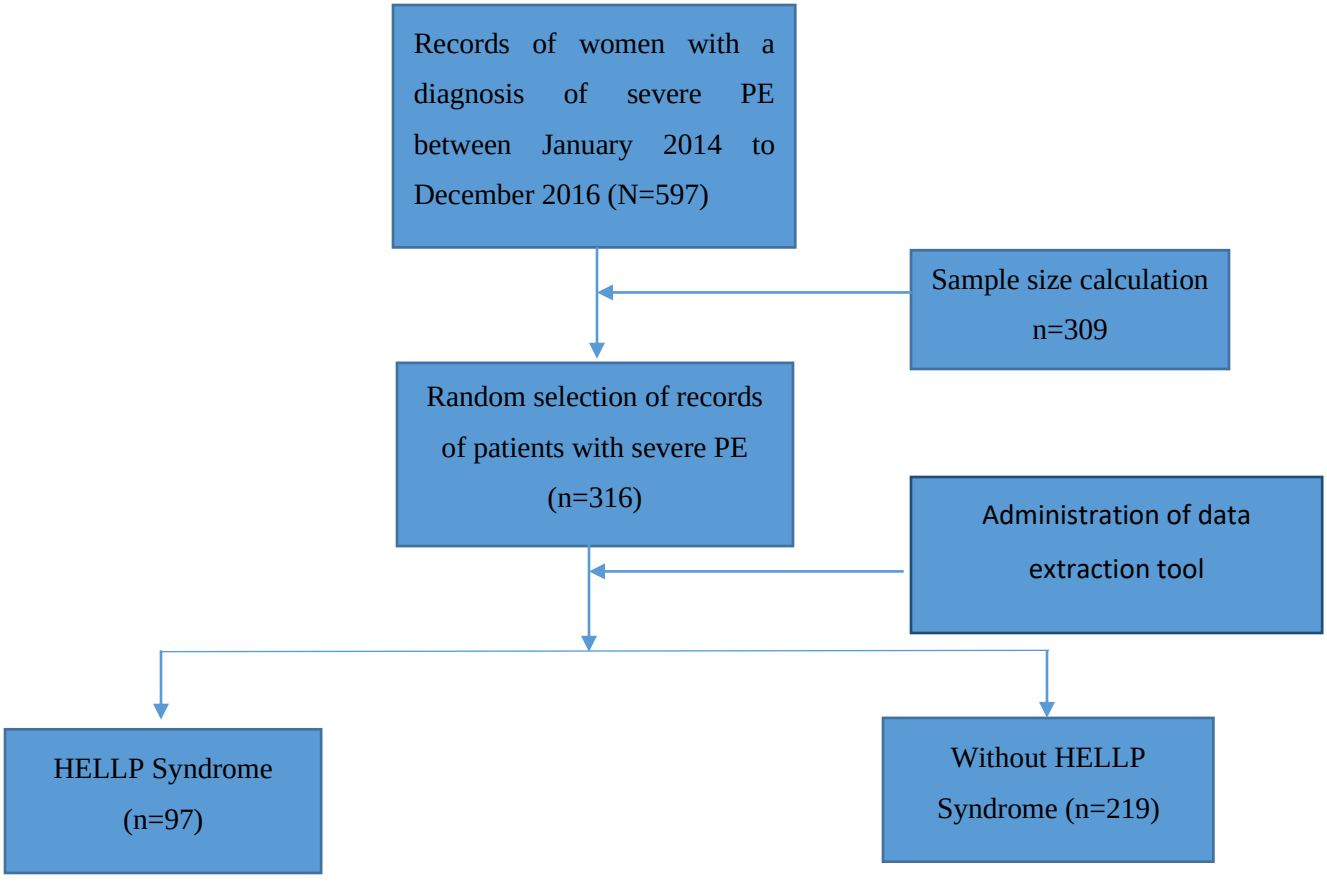
Statistician	30,000
Stationery	15,000
Contingencies	15,000
Research fee	2,500
Research assistants	30,000
Printing and binding	15,000
Total	**107,500**

CHAPTER FOUR: RESULTS

The objective of this study was to determine the factors and clinical features associated with the development of HELLP syndrome among patients with PE with severe features at the Kenyatta National Hospital.

A total of 316 records of patients with PE with severe features managed at KNH between 1st January 2014 and December 2016 were retrieved for this study. Out of these, 97 cases (31%) and 219 controls (69%) were analyzable for this study. For the cases, the mean age was 29.5 years and the mean gestational age at diagnosis was 32 weeks.

STUDY FLOW CHART



The results are presented below as per the specific objectives of the study.

Table 1: Sociodemographiccharacteritics associated with development of HELLP syndrome among patients with PE with severe features in KNH.

Variable		Cases PE + HELLP	ControlsPE - HELLP	OR (95% CI)	P value
Education Level	Post Primary	63(28)	162 (72)	1.5	0.088
	Primary	33 (38)	54 (62)	(0.93 – 2.65)	
Marital Status	Married	80(30)	184 (70)	1.1	0.733
	Single	17(33)	35 (67)	(0.59 – 2.11)	
Age	< 25years	28(39)	44 (61)	0.61	0.077
	≥ 25 years	68 (28)	175 (72)	(0.35 – 1.06)	

There was no statistically significant association between the education level (p=0.088), marital status (p=0.733) or patients age (p=0.077), and development of HELLP syndrome as shown in the table above.

Table 2: Obstetric characteristics associated with development of HELLP syndrome among patients with PE with severe features in KNH.

Variable		Cases PE + HELLP	Controls PE - HELLP	OR (95% CI)	P value
Parity	Multipara	76 (32)	160 (68)	0.75	0.318
	Primipara	21 (26)	59 (74)	(0.46- 1.32)	
Gestational age	<28weeks	33 (38)	54 (62)	0.625	0.076
	≥28weeks	63 (28)	165 (72)	(0.37 – 1.05)	
History of preeclampsia/hypertension	Yes	14 (23)	46 (77)	0.74	0.74
	No	74 (33)	154 (67)		

There was no statistically significant association between parity (p=0.318), gestational age at diagnosis, (p=0.076) and a history of pre-eclampsia/hypertension (p=0.389) and development of HELLP syndrome, as shown in the table above.

Table 3: Clinical features associated with development of HELLP syndrome among patients with PE with severe features in KNH.

Variable		Cases PE + HELLP	Controls PE - HELLP	OR (95% CI)	P value
History of headache	Yes	62 (30)	147 (70)	0.86 (0.521.43)	0.579
	No	34 (32)	72 (68)		
History of blurring of vision	Yes	24 (29)	59 (71)	0.94 (0.55-1.62)	0.847
	No	71 (31)	155 (69)		
History of epigastric pain	Yes	55 (39)	85 (61)	**2.06 (1.27-3.35)**	**0.003**
	No	42 (24)	134 (76)		
Systolic Pressure	140-159	12 (46)	14 (54)	0.45 (0.19-1.02)	0.051
	≥160	66 (28)	172 (72)		
Diastolic Pressure	90 – 109	23 (33)	47 (67)	0.766 (0.23-1.39)	0.37
	≥ 110	51 (27)	136 (73)		

There was a statistically significant association between having a history of epigastric pain and development of HELLP syndrome (p=0.003). There was no statistically significant association between having a history of blurred vision and a history of headache with development of HELLP syndrome (p=0.579, p=0.847 respectively). There was also no statistically significant association between systolic and diastolic blood pressure and the development of HELLP syndrome (p=0.051, p=0.37 respectively) as shown in the table above.

Table 4: Laboratory features associated with development of HELLP syndrome among patients with PE with severe features in KNH

Variable		Cases PE + HELLP	Controls PE - HELLP	OR (95% CI)
Proteinuria	Less than 1+	23 (34)	45 (64)	0.77
	More than 1+	54 (28)	137 (79)	(0.47 – 1.40)
Creatinine	Less than 110	53 (23)	179 (77)	**3.8**
	More than 110	44 (53)	39 (47)	**(2.245-6.466)**

Patients with creatinine levels of more than 110micromoles/ml were more likely to develop HELLP syndrome (p, <0.0001). There was no statistically significant association between levels of proteinuria of more than 1+ and the development of HELLP syndrome (p = 0.390), as shown in the table above.

Table 5: Multivariate analysis to compare the factors associated with the development of HELLP syndrome among patients with PE with severe features in KNH

		Odds Ratio	**95% C.I.**		**P value**
			Lower	Upper	
	High creatinine	3.466	2.024	5.935	**<0.0001**
	History of epigastric	.586	.353	.974	**0.039**
	Constant	.403			<0.0001

A logistic regression was performed on the factors that were significantly associated with development of HELLP syndrome (positive history of epigastric pain and high levels of creatinine level more than 110). The logistic model explained 12.5.0% (Nagelkerke R^2) of the variance in the development of HELLP syndrome and correctly classified 100% of cases. Patients with creatinine levels more than 110 were 3.47 more likely to develop HELLP syndrome (p, <0.0001, 95% CI, 2.024, 5.935). In addition, patients without a history of epigastric pain were 41.4% less likely to develop HELLP syndrome (p, 0.039, 95% CI 0.353, 0.974).

DISCUSSION

This study sought to determine the factors associated with the development of HELLP syndrome among patients with pre-eclampsia with severe features in Kenyatta National Hospital.

In the study, 31% of patients with pre-eclampsia with severe features had HELLP syndrome while 69% had no HELLP syndrome.

In this study, the variables that showed statistically significant associations with the development of HELLP syndrome included: a positive history of epigastric pain, and creatinine levels of more than 110 micromoles/ml.

There was no statistically significant association between education level and the development of HELLP syndrome.

There was no statistically significant association between marital status and the development of HELLP syndrome.

There was no statistically significant association between patients' age and the development of HELLP syndrome. A study done by Tugba et al in Turkey found that there was no statistical difference in maternal age in patients with HELLP syndrome. On the contrary, a study by Sibai et al in USA found that most patients with HELLP syndrome were above 25 years old.

This study did not show any association between parity and the development of HELLP syndrome. On the contrary, a study done by Williams et al in Canada found that the incidence of HELLP syndrome was significantly lower in multiparous women compared to primigravidas.

The study did not show any association between gestational age and the development of HELLP syndrome.Haram et al in Norway and Sibai et al in USA found a higher incidence of HELLP syndrome between 27th and 37th weeks of gestation.

There was no association between having a history of PE/HELLP and the development of HELLP syndrome. A study done by Malstrom et al in Sweden found that patients who had a history of HELLP syndrome or preeclampia in a previous pregnancy had a higher incidence of HELLP syndrome.

There was a statistically significant association between having a history of epigastric pain and development of HELLP syndrome. Similarly, Tugba et al in Turkey found that epigastric pain levels were higher in patients with HELLP syndrome compared to those without HELLP syndrome.

There was no association between having a history of blurred vision and headache and the development of HELLP syndrome in this study. There were no studies found that looked at the association between these symptoms and the development of HELLP syndrome.

Patients with creatinine levels of >110micromoles/ml were 3.8 times more likely to develop HELLP syndrome compared to those with lower creatinine levels. On the contrary, Tugba et al in Turkey found that there was no statistically significant association between creatinine levels and development of HELLP syndrome.

There was no statistically significant association between high levels of proteinuria and the development of HELLP syndrome in this study.

The main limitations of the study were missing information from files.

The strengths of the study were the the non-invasive nature as there was no patient contact or interventional procedures involved and the study adopted a case control design which has a high level of evidence and is suitable for studying rare outcomes such as HELLP syndrome.

CONCLUSION

The mean age of patients with PE with severe features and HELLP syndrome was 29.5 years.

Having a history of epigastric pain appears to predispose patients with PE with severe features to HELLP syndrome. In addition, elevated creatinine levels appears to be a risk factor to the development of HELLP syndrome in patients with PE with severe features.

RECOMMENDATIONS

1. Patients with pre-eclampsia with severe features who present with complains of epigastric pain or those noted to have elevated creatinine levels should be closely monitored for early identification of HELLP syndrome.
2. Need to undertake a prospective cohort/ longitudinal study to better examine this important yet poorly understood topic.

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APPENDICES:

Appendix 1: DATA COLLECTION WORKSHEET

SECTION A: PRELIMINARY INFORMATION

PATIENT CODE ☐☐☐☐

DATE OF ADMISSION (DD MM YYYY) ☐☐☐☐☐☐☐☐

SECTION B: DEMOGRAPHIC INFORMATION

1. What is your marital status?
   1……Single☐
   2…….Married☐
   3…….Other☐
2. .What is your level of education?
   1……None☐
   2…….Primary☐
   3…….Secondary☐
   4……..Post-Secondary☐
3. What is your age? ☐☐ 1…….....15-21 years
   2…….22-30 years
   3……31-40 years
   4……41-49 years

SECTION C: OBSTETRIC CHARACTERISTICS

4. What was the gestational age at diagnosis (weeks) ☐☐
   1…….....20-24 weeks
   2…….25-29 weeks
   3……30-34 weeks
   4……>35 weeks
5. What is the parity: 1……..…Primigravida☐
   2……..….Multipara☐
   3……Grand Multipara☐
6. Is there history of antenatal use of antihypertensives: 1……..Yes ☐
   2…… No ☐
7. If yes to 6 above, which antihypertensives
   1……Methyldopa Yes ☐ No ☐
   2…….Nifedipine Yes ☐ No ☐
   3…….Any other antihypertensive Yes ☐ No ☐
8. Is there history of preeclampsia/hypertensive disease in previous pregnancy/pregnancies?
   1……Yes ☐
   2……..…No ☐
9. Is there presence of other chronic disease: 1…….Yes ☐ 2…….. No ☐

SECTION D: PRESENTATION : Is there a:

10. history of headache: 1……. yes ☐2……. no ☐

11. history of blurring of vision 1……..yes ☐2 ……no ☐

12. history of nausea / vomiting: 1……...yes☐2…….. no☐

13. history of malaise: 1…….. yes ☐2…… no ☐

14. history of epigastric / right upper quadrant pain: 1……yes ☐ 2……..no ☐

DURING THE ADMISSION PERIOD:

15. What was highest systolic bp: (mmHg) ☐☐☐ 1…….<140
2……..141-159
3……>160
16. What was the highest diastolic bp: (mmHg) ☐☐☐ 1…….<90
2……91-109
3…….....>110
17. Was there edema: 1……..Yes☐ 2……..No☐
18. What was the level of proteinuria: 1……None☐
2…….1+☐
3……2+☐
4…….3+☐
19. LOWEST HAEMOGLOBIN LEVEL: (g/dL) ☐☐
20. LOWEST HAEMATOCRIT LEVEL: (%) ☐☐
21. LOWEST PLATELET LEVEL($X10^{3)}$☐☐☐☐
1……<49
2…….50-99
3……100-150
4…….>150
22. HIGHEST AST (U/L) ☐☐☐☐ 1……..<40
2……41-70
3…….>70
23. HIGHEST ALT (U/L) ☐☐☐☐ 1……..<40
2……41-70
3…….>70
24. HIGHEST BILIRUBIN LEVELS (mg/dL) ☐☐☐☐ 1…….<600
2…….>600
25. PERIPHERAL BLOOD SMEAR: 1……Normal ☐
2…… Abnormal ☐
3….Not Done☐
26. HIGHEST LDH (U/L) ☐☐☐

27. HIGHEST UREA (mmol/L) ☐☐☐☐

28. HIGHEST CREATININE (micromoles/ml) ☐☐☐☐

29. Special notes

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Appendix 2: DATA QUALITY CONTROL METHODS ADAPTED IN THIS STUDY*

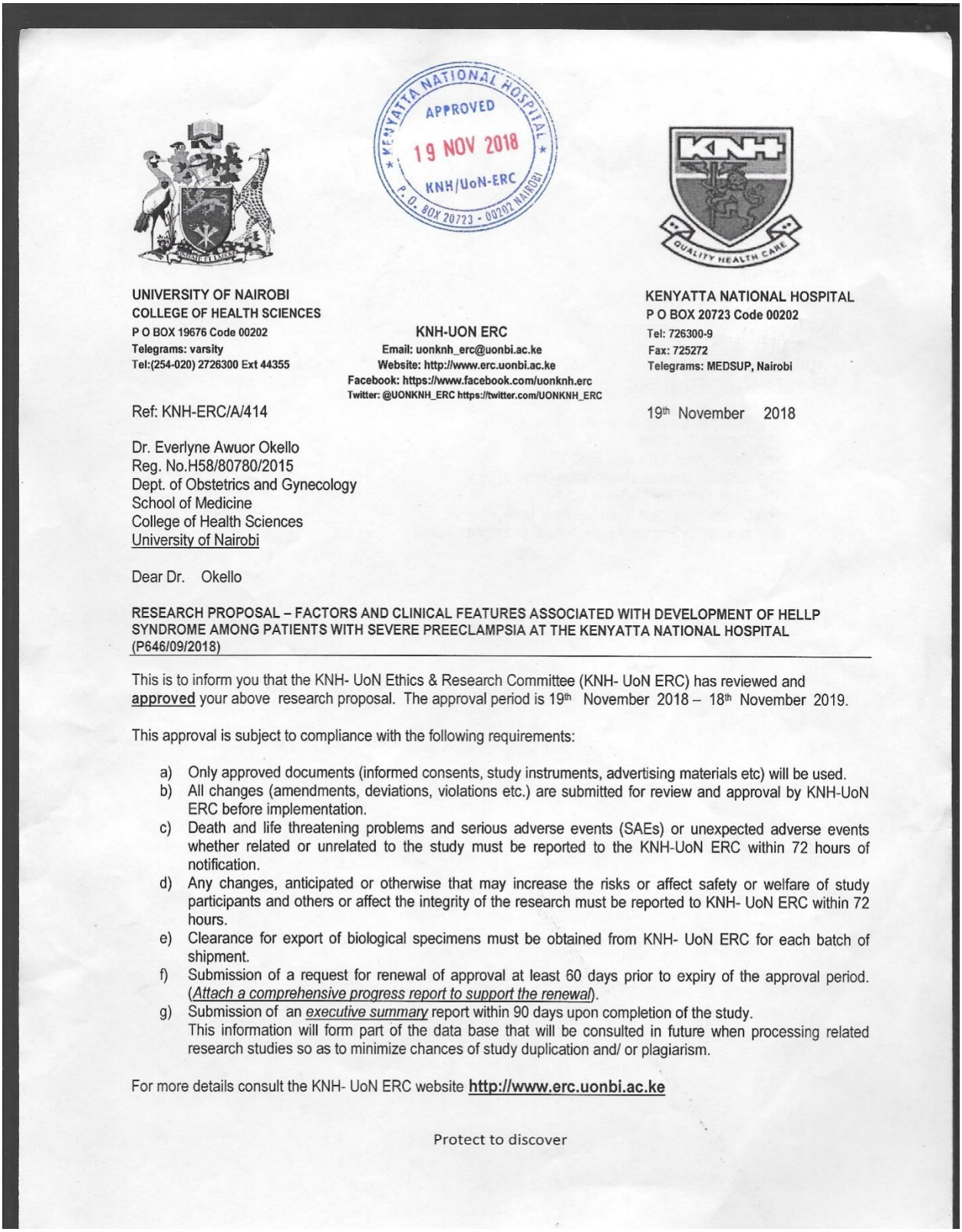
Table 1

Data quality control methods for QI projects

Project phase	Challenge question
Project design	Are the aims of the project clearly stated?
	Is a valid definition and measurement system available for the required data?
	Is there a clear focus on quality, rather than quantity, of data?
Data collection	Is a standardized data collection form created?
	Are data items clearly defined and written instructions provided for collecting each data item?
	Are staff adequately trained to collect data?
	Are QA reviews completed?
	Is an electronic database used for data management?
	Are sufficient database controls in place to identify errors?
	Is there a back-up routine for the electronic database?
Data management	Have data been evaluated using basic statistics?
	Has there been a comprehensive review for missing data and methods to minimize missing data?
Data analysis	Are missing data reported and appropriate methods used to account for it?
	Have potential outliers been identified and evaluated?
	Have appropriate methods been used to provide summary measures of the project results?
	Have measures of precision been presented with the study results?
	Have appropriate methods been used to evaluate the impact of factors that may confound the results?

*Needham, D. M., Sinopoli, D. J., Dinglas, V. D., Berenholtz, S. M., Korupolu, R., Watson, S. R., … Pronovost, P. J. (2009). Improving data quality control in quality improvement projects. *International Journal for Quality in Health Care*, *21*(2), 145–150. =-

Appendix 3: ETHICAL APPROVAL



KENYATTA NATIONAL HOSPITAL
APPROVED
19 NOV 2018
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Ref: KNH-ERC/A/414

19th November 2018

Dr. Everlyne Awuor Okello
Reg. No.H58/80780/2015
Dept. of Obstetrics and Gynecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Okello

RESEARCH PROPOSAL – FACTORS AND CLINICAL FEATURES ASSOCIATED WITH DEVELOPMENT OF HELLP SYNDROME AMONG PATIENTS WITH SEVERE PREECLAMPSIA AT THE KENYATTA NATIONAL HOSPITAL (P646/09/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 19th November 2018 – 18th November 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Protect to discover

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH-UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine,UON
The Chairperson, Dept. of Obs/Gynae, UoN
Supervisors: Dr.Francis Xavier Odawa, Dr.Stephen Mutiso