# ASSOCIATION BETWEEN SERUM URIC ACID AND FETOMATERNAL OUTCOMES IN PREECLAMPTIC WOMEN AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET KENYA

**BY**

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**MOI UNIVERSITY**

# DECLARATION

**Declaration by candidate:**

I declare that this is my original work and that it has not been presented in any academic or research institution for award of degree in this university or any other university for the award of any degree or academic credit. No part of this thesis may be reproduced without prior written permission of the author, supervisors and or Moi University.

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## DEDICATION

This study is dedicated to all Obstetricians and Gynecologists for their invaluable work in ensuring quality maternal health

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## DEFINITION OF TERMS

**Pre-eclampsia:** Is the new onset of Hypertension (arterial blood pressure >140/90mm of Hg) and proteinuria (≥ 0.3 grams (300 mg in 24 hours) or a new onset of Hypertension and a significant end organ dysfunction with or without proteinuria after 20 weeks gestation or postpartum in a previously normotensive woman.

**Proteinuria**: Proteinuria ≥ 0.3 grams (300 mg) of protein in a 24-hour urine sample or a SPOT urinary protein to creatinine ratio ≥0.3 or a urine dipstick reading of 1+ or greater.

**Preeclampsia with severe features**: is diagnosed when systolic pressure ≥160 mmHg or diastolic pressure ≥110 mmHg or both with or without proteinuria, headache, visual changes, upper abdominal pain, oliguria, increased serum creatinine and liver transaminases and thrombocytopenia (<100,000).

**Uric acid**: Is a product of metabolic breakdown of purine nucleotide and a normal component of urine excreted through the kidneys. It can be measured in blood, where a serum value < 340 Umol/l is considered normal and serum value above or equal to 340 is considered high is pregnancy.

**Perinatal:** Is defined by WHO as a period when a fetus attains viability to end of seventh complete day of life. And in my study it meant a period when a fetus attains viability to the first complete day of life (immediate perinatal period).

**Pregnancy outcomes**: It is the end results or final results of a pregnancy, and it includes maternal and fetal outcomes.

The fetal outcomes include: Low birth weight, preterm birth, intrauterine growth restrictions, birth asphyxia and Low APGAR scores, still birth, intrauterine death, and neonatal death.

**Maternal outcome include:** Premature rupture of membranes (PPROM), placenta abruption, HELLP syndrome, Eclampsia, induction of labor, Modes of deliveries, renal failure, pulmonary hypertension, Hospitalization time and maternal death.

Fetal growth restrictions (FGR): Is a fetus that does not achieve the expected in utero growth potential due to genetic or environmental factors. It is a growth at the 10th or less percentile for weight of all fetuses at that gestation age.

**Low Birth weight**: An infant less than 2500 grams measured in the first hour after birth as per WHO,

**Intrauterine death:** A Neonate born with no signs of life at or after 28 weeks of gestation according to World Health Organization (WHO).

Stillbirth: Is defined by WHO as a neonate born with no signs of life at or after 28 weeks gestation.

**Pre-term birth**: Birth of a live infant before 37 completed weeks of gestation.

Singleton birth: Is birth of only one child during single delivery with a gestation of 20 weeks or more.

**Induction of labor**: It is the process of artificially stimulating the uterus to start labor. It is usually performed by administering oxytocin or prostaglandins to pregnant woman, or by artificially rupturing the membranes.

## ABBREVIATIONS

| | |
|---|---|
| **ANW** | Antenatal Ward |
| **DPB** | Diastolic Blood Pressure |
| **EUA** | Elevated uric acid |
| **FIGO** | International Federation of Gynecology and Obstetrics |
| **HELLP** | Hemolysis elevated Liver Enzymes, Low Platelet count |
| **ICU** | Intensive Care Unit |
| **IOL** | Induction of Labor |
| **ISSHP** | International Society for the Study of Hypertension in Pregnancy |
| **IUGR** | Intrauterine Growth Retardation |
| **LBW** | Low Birth Weight |
| **LW** | Labor Ward |
| **MM** | Maternal Mortality |
| **MTRH** | Moi Teaching and Referral Hospital |
| **NICU** | Neonatal Intensive Care Unit |
| **NUA** | Normal uric acid |
| **PE** | Preeclampsia |
| **PNW** | Post Natal Ward |

| | |
|---|---|
| **PROM** | Premature Rupture of Membranes |
| **SBP** | Systolic Blood Pressure |
| **SUA** | Serum Uric Acid |
| **WHO** | World Health Organization |

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## ABSTRACT

**Background:** Preeclampsia (PET) is one of hypertensive disorder of pregnancy with a high mortality and morbidity worldwide. Uric acid is a metabolic end product of purines found elevated in preeclamptic patients and it's closely related to occurrence of adverse maternal and immediate perinatal outcomes (pregnant outcomes). Its use in pregnant complicated with PET is controversial.

**Objective:** To describe the association between serum uric acid and fetomaternal outcomes among preeclamptic women in Moi teaching and referral hospital (MTRH).

**Methods:** This was a cross-section comparative study carried out at MTRH post natal ward. Consenting preeclamptic women were recruited into 55 PET women with elevated uric acid ( > 340mmol/l) and 110 PET women with normal uric acid (<340mml/l) and a systematic sampling technique was used to achieve sample size in each group. Researcher administered structured questionnaire was used to collect data on maternal and feta variable. Fetal variables included; birth weight, fetal growth restriction, Apgar score at five minutes, admission in NICU. Maternal variables included; placenta abruption, organ failure, admission to ICU and severity of PET. PET was classified into PET without severe features and PET with severe feature that included systolic Bp of >160mmgh or diastolic Bp of >110mmgh, thrombocytopenia of <100,000/mL and end organ damage. Descriptive data was summarized as means and corresponding standard deviation. Chi square and Fisher's exact test were done at bivariate level to compare uric acid levels and other categorical variables. Multivariable logistic regression was done to determine the factors associated with elevated uric acid. The data was presented using odds ratio with 95% confidence interval and a statistical significance level set at p-value < 0.05. The study duration was one year from August 2021 to August 2022. Approval of the study was sought from relevant authorities.

**Results:** A total of 165 participants were recruited in the study, 55 and 110 women in elevated uric acid (EUA) and normal uric acid (NUA) arm respectively. Women with PET with severe features had significantly high uric acid compared to women with PET without severe features (492.8±74.1 vs 296.3±41.5) respectively. The magnitude of adverse perinatal in preeclamptic women with elevated uric acid (EUA) was 85.7% low APGAR score, 73.7% low birth weight, 67.8% NICU admission and 77 % for fetal non viability syndrome. Majority (62.7%) of PET women with EUA were more likely to develop severe maternal complications (p<0.001) like HELLP syndrome and preterm labor.

In adjusted model, elevated uric acid (340umol/I) once adjusted for preeclampsia grades, maternal age, parity, and gestation age, it revealed an increased risk in low APGAR scores ( aOR 4.63,95% CI,1.57-13.71), low birth weight (aOR 4.08,95% CI,1.62-10.29), preterm labor (aOR 6.27,95% CI, 2.07- 18.95) and severe maternal complications (aOR 3.52,95% CI, 0.91-13.61).

**Conclusion:** Higher serum uric acid levels was associated with disease severity, poor perinatal outcome and maternal outcomes.

**Recommendation:** We recommend the use of serum uric acid in evaluating preeclampsia severity, perinatal and maternal outcomes.

# CHAPTER ONE

## 1.0 INTRODUCTION

### 1.1 Background of the study

Worldwide maternal mortality (MM) is unacceptably high. About 295 000 women died during and following pregnancy and childbirth in 2017. The vast majority of these deaths (94%) occurred in low-resource settings, and most could have been prevented (WHO; 2019).

Globally, about five to ten percent of women experience hypertensive disorders in pregnancy (HDPs) (Janani F, at-el 2017), making it the third leading cause of maternal mortality and morbidity after severe bleeding and infections. HDPs include pre-eclampsia eclampsia, gestational hypertension, and chronic hypertension.

Pre-eclampsia (PE) is a pregnant- specific syndrome characterized by new onset of hypertension and proteinuria after 20 weeks' pregnancy gestation with anew onset of end organ disorder (ACOG 2018). Hypertension is defined as either systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90mm Hg or greater, or both, taken four hours apart (ACOG hypertension in pregnancy guidelines, 2019). It is classified as non-severe if systolic blood pressure is below 160 mm Hg or diastolic blood pressure is below 110 mm Hg without end organ failure taken four hours apart. Blood pressures greater than 160 mm Hg (systolic) or 110 mm Hg (diastolic) are considered severe and can be confirmed within a shorter interval to facilitate timely therapy (ACOG, 2019). Proteinuria is diagnosed as protein urine excretion of equal to or greater than 300mg in 24 hours (24-hour urine sample). It can also be diagnosed if the ratio of measured protein to creatinine in single voided urine is 0.3 or more (ACOG, 2019).

According to Management of severe PET and eclampsia; Guidelines and audit implementation network (2012), severe PET is defined as diastolic Blood Pressure (BP) of at least 110 mm Hg or systolic blood pressure of at least 160 mm Hg, and/or symptoms, and/or biochemical and/or hematological impairment, which is in keeping with the ACOG 2019 guidelines. Severe features of PET include systolic blood pressure of 160mm Hg or higher or diastolic blood pressure of 110mm Hg (or both), thrombocytopenia (platelet count of less than 100,000/micro liter), impaired liver functions (elevated liver enzymes to twice normal or severe persistent right upper quadrant or epigastric pains unresponsive to medication, with no other attributable cause), pulmonary edema, new onset of cerebral or visual disturbance and progressive renal insufficiency, which is, serum creatinine greater than 1.1 mg/dl or doubled serum concentration in the absence other renal disease (ACOG, 2019).

**Severe features of preeclampsia (≥1 finding)**

1. Systolic blood pressure of 160 mm Hg or diastolic blood pressure of 110 mm Hg on 2 occasions at least 4 hours apart while the patient is bed rest (unless antihypertensive therapy is initiated before this time)
2. Thrombocytopenia (platelet count <100,000/mL).
3. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both.
4. Progressive renal insufficiency (serum creatinine concentration>1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal diseases)

5. Pulmonary edema
6. New-onset cerebral or visual disturbances

**(Adapted from the American College of Obstetricians and Gynecologists 2022)**

PET affects 2-8% of all pregnancies, and remains a leading cause of maternal and perinatal morbidity and mortality globally (ACOG 2019). Majority of the estimated 70,000 to 80,000 annual maternal and 50, 000 annual perinatal preeclampsia related deaths occurs in low and middle-income countries (LMICs) such as Kenya (Duley L at el 2015).

In Kenya, the 2014 confidential inquiry into maternal death revealed HDP as the third leading cause of maternal mortality, accounting for 20 % of maternal deaths (MOH 2017). The prevalence of preeclampsia in Kenya is estimated to be 5.6% to 6.5%, although proportions are likely to be higher in rural areas (KNH 2015). And the incidence in Kenya is about 2.3% (Itoh et al., 2017).

PET is a common complication of pregnancy that greatly affects the fetal and maternal mortality and morbidity throughout the world. It has a devastating effect on pregnant women, their fetuses, and newborns. Women with pre-eclampsia suffer severe morbidity and mortality due to placental abruption, pulmonary edema, acute renal failure, and other organ damage (ACOG 2013). Moreover, newborns of women with pre-eclampsia have approximately twice the risk of neonatal death, and increased risks of low Apgar scores, intrauterine growth restriction, seizures, neonatal encephalopathy, and neonatal intensive care admission (W Szymonowicz 2013).

This pregnancy-specific syndrome can affect virtually all organs in the body. Despite thorough characterization of preeclamptic syndrome and a suite of contributing

circulating factors, the mechanism underlying the pathogenesis of this troubling condition remains nebulous. The endothelial dysfunction is considered to play a central role in pathophysiology of pre-eclampsia (Ware DB, at-el 2001). However there are no screening tests reliable enough to diagnose preeclampsia and hence institute timely intervention to prevent complications.

Hyperuricemia is one of the common findings in pre-eclampsia. The uric acid level in pre-eclamptic women is increased before the onset of hypertension and proteinuria and it is a potent mediator of inflammation that stimulates monocytes to produce pro-inflammatory cytokines IL-1β, IL-6, TNF-α which promotes endothelial dysfunction per se which could promote hypertension, vascular disease and renal disease (Toshniwal S, at-el 2017). It is one of the most sensitive indicators of disease severity in preeclampsia and can be of great help in monitoring the course of the disease process (Pagana KD at-el 1998). Some studies have demonstrated a correlation between elevated maternal serum uric acid and adverse maternal and fetal outcomes (Tomoko H, at-el 2019). According to some studies uric acid (UA) is not a predictor of pregnant outcomes whereas another group of researchers indicate uric acid as a predictor of pregnant outcome hence its utility in pregnant complicated with PET is controversial.

Uric acid is an end product of purine degradation catalyzed by the enzyme xanthine dehydrogenase/xanthine oxidase. In normal pregnant women serum uric acid concentration initially falls 25-30% due to elevation in renal clearance secondary to increased glomerular filtration rate (GFR) or reduced proximal tubular reabsorption due to changes in its production rate. Later in pregnancy, the serum uric acid levels increase due to fetal production, decreased uric acid clearance, and decreased binding to albumin (Hill IM, 1978). In preeclampsia, several factors contribute to the elevated

level of uric acid: decrease glomerular filtration rate, increased tissue breakdown, acidosis and increased activity of the enzyme xanthine dehydrogenase/xanthine oxidase (Jonson et al 2014).

Uric acid is filtered, reabsorbed, and secreted by the kidney with its concentration correlating with the occurrence and the severity of PET and resolves after delivery. In early pregnancy, serum uric acid level falls, often to 3mg/dl. During the third trimester, the serum uric acid level may reach up to 4-6mg/dl. Therefore hyperuricemia is defined as serum uric acid of more than 6mg/dl in third trimester in PET women (Jonson et al 2014).

Clinical prediction of PET may facilitate initiation of timely management to avert mortality and morbidity in the mother and infant associated with preeclampsia. In our context, several studies have been done on pregnancy-induced hypertension in terms of diagnosis, the fetomaternal outcome in relation to gestational age, the severity of the disease, and proteinuria and uric acid in developed countries (Kondareddy et al 2016). However, only a few studies have been done in low and middle income countries (LMICs) in relation to uric acid concentration and fetomaternal outcome. Therefore, the aim of the present study was designed to find the association between the levels of serum uric acid in pregnant women with the severity of preeclampsia and the maternal and fetal outcomes.

## 1.2 Problem Statement

According to the 2014 confidential inquiry into maternal death in Kenya show that preeclampsia is the third leading cause of maternal mortality, accounting for 20 percent of maternal deaths (MOH 2017). The incidence of preeclampsia is about 0.3% while the prevalence is 6.1% in Kenya (Otieno D 2012), though proportions are likely to be higher in rural areas.

Considering hypertensive disorder of pregnancies (HDPs) including preeclampsia (PET) are recognized among the leading causes of maternal and newborn mortality and morbidity in Kenya and to that extend in MTRH, there is an increasing emphasis on early detection and management of this condition. Late detection and poor management in primary healthcare facilities negatively affects newborn and maternal health outcomes.

The most common reason for such a high maternal and perinatal morbidity and mortality associated with PET is the unavailability of precise and specific test that can identify pregnant women at risk of developing preeclampsia (Von Dadelszen P, 2016). One such biochemical marker that can be used to assess the severity of PET and its effect on the maternal and fetal outcome to a large extent is maternal serum uric acid level that has been shown in many studies to be elevated in Pregnancy complicated with preeclampsia. But there are uncertainties around the use of serum uric acid in management of PET women.

Despite the problem having increased adverse maternal and fetal effects in Kenya and to an extend MTRH, there is a paucity of information available about uric acid as a predictor of maternal and fetal outcomes in pre-eclampsia in Moi teaching and referral hospital in Eldoret Kenya.

## 1.3 Justification

Preeclampsia is a known life- threatening complication for both the affected mother and the unborn infant. Early detection and management of pre-eclampsia is essential. Efforts have been focused on improving maternal and perinatal outcomes based on the maternal clinical symptoms and laboratory markers. However little attention has been directed on use of biomarkers such as maternal uric acid levels, to determine maternal and perinatal outcomes especially in resource limited setting like Kenya.

This study which associated the maternal uric acid levels and outcomes among pregnant women admitted with preeclampsia at Moi teaching and referral hospital is going to act as a baseline to help synthesize management plan and improve management protocol and overall maternal and neonatal outcomes.

## 1.4 Significance of the study

1. The results of the study will act as a guide in formulating policies for prevention of preeclampsia, its severity, and fatality with the existing resources in MTRH.
2. Has contributed to existing knowledge and understanding about the adverse effect of pre-eclampsia on the mother and the fetus and helped increase emergency obstetric care and functioning of the health facility based on evidence.
3. Is going to improve quality of life of the baby and the mother affected with preeclampsia

## 1.5 Research question

1. Is there an association between serum uric acid level with disease severity and maternal and perinatal outcomes in women with preeclampsia at MTRH

## 1.6 Hypothesis

**Null Hypothesis:** There is no relationship between high uric acid levels with disease severity and maternal and perinatal outcomes.

**Alternative Hypothesis:** There is a relationship between high uric acid levels with disease severity and maternal and perinatal outcomes.

## 1.7 Objectives

### 1.7.1 Broad objectives

The purpose of the study is to describe the relationship between serum uric acid levels with disease severity, maternal and immediate perinatal outcomes among PET women in Moi teaching and referral hospital in Eldoret, Kenya.

### 1.7.2 Specific objectives

1. To determine the association between serum uric acid levels and PET severity in Moi teaching and referral hospital (MTRH).
2. To compare serum uric acid levels and immediate perinatal outcome among PET women with elevated UA levels and normal UA levels in MTRH.
3. To compare serum uric acid levels and maternal outcome among PET women with elevated UA levels and normal UA levels in MTRH.

## CONCEPTUAL FRAMEWORK

**Fig I: show the of association between serum uric acid and fetomaternal outcomes**

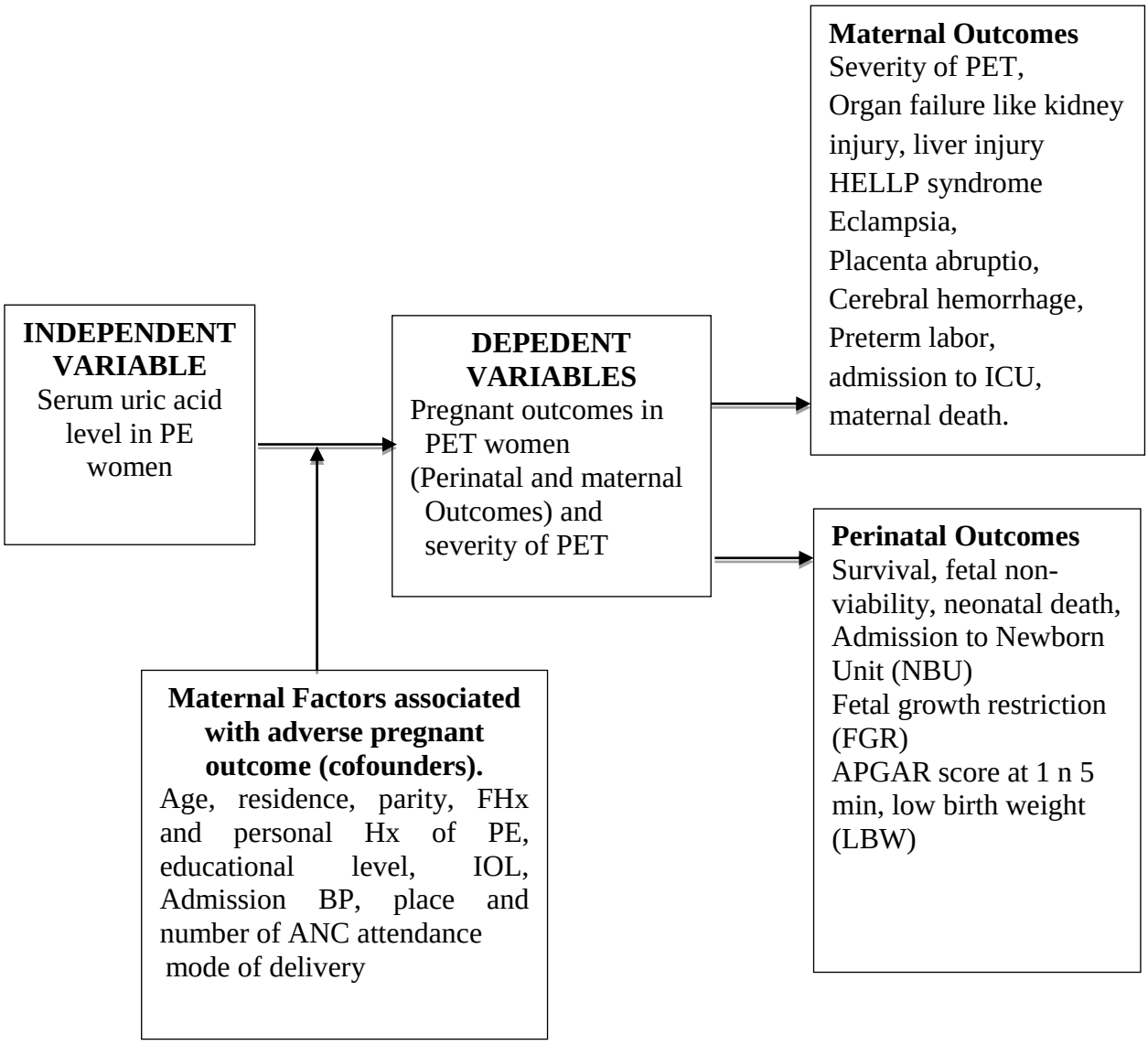



**Figure 1: Conceptual framework**

# CHAPTER TWO

## 2.0 LITERATURE REVIEW

### 2.1 Introduction

#### 2.1.1 Overview of maternal and perinatal mortality and morbidity

Maternal and perinatal mortality and morbidity rate remain high to date and has been a concern by many development agencies since 1980 as it is a key indicator for international development. For instance, in 1980's the World Health Organization (WHO) estimated that approximately half a million women died annually (Brown et al., 2013). While in 1990's it was estimated that around 5 million newborns died (Ma et al., 2019).

The past three decades have seen concerted efforts initiated by different organization and development agencies to reduce maternal and fetal mortality and morbidity. In 1987 the first conference on Safe Motherhood held in Nairobi put measures to combat maternal deaths such as making family planning universally available, providing prenatal care and trained assistance at delivery, and ensuring access to emergency obstetric care. Subsequently other conferences with similar objectives such as the World Summit for Children in 1990, the International Conference on Population and Development in 1994, and the Fourth World Conference on Women in1995 were held (Brown et al., 2013). Similarly, in 2000, the Millennium Development Goals articulated measures aimed at reducing socio-economic inequalities in areas such as poverty, education, gender equality, child mortality, maternal health, and infectious diseases, so as to achieve universal health and reduce maternal and fetal mortality by the end of 2015 (Kyei-Nimakoh et al., 2016).

These focused measures seemed to have yielded progress towards reduction in maternal deaths. As a result, global maternal and fetal mortality reduced by 38% that is from 342 deaths to 211 and 51% i.e. 3000 to 1800 deaths per 100,000 live births between 2000 and 2017 respectively (Ma et al., 2019; WHO, UNICEF, 2019). Although there was significant reduction in MM and FM in Sub Saharan Africa that is from 870 deaths to 533 and 3600 to 3000 deaths per 100,000 live births within the same period, there region still accounts for high rate of maternal mortality (MM) 84% and fetal mortality 79% when compared to other regions across the globe (Callister and Edwards, 2017). In Kenya for instance, the MM rate is estimated at 342 deaths per 100,000 live births. Although there has been substantive progress towards reduction in MM, the rate is below the required needed to achieve the Sustainable Development global goal of 70 maternal deaths per 100,000 live births and 12 deaths per 100 live births for fetal mortality (Ma et al., 2019; WHO, UNICEF, 2019). Maternal and fetal deaths are preventable and manageable if detected early. A key advancement to further reduce MM rates is to understand the causes so as to design effective health policies (Say et al., 2014).

### 2.1.2 Causes of maternal and fetal mortality

Causes of MM have widely been studied and documented and they range from indirect and direct (Brown et al., 2013; Lumbiganon et al., 2014; Sageer et al., 2019; Say et al., 2014; Yakasai and Gaya, 2011; Yego et al., 2014). Indirect causes account for 27.5% and are aggravated by conditions related to diseases such as malaria, heart disease, diabetes, HIV and anemia among others (Lumbiganon et al., 2014). Other indirect causes are associated with socio-economic conditions and include inadequate human resource for health, delay in seeking care, inadequate equipment, lack of ambulance transportation, and delay in referrals services (Sageer et al., 2019). Direct

causes attributed to obstetric account for 73% of the deaths and are caused by conditions such as hemorrhage-27.1%, hypertensive disorders-14.0%, Sepsis-10.7%, Abortive outcomes-7.9% and embolism and other conditions-12.8% (Black et al., 2016).

Fetal mortality rates are associated with factors such as preterm birth and Intrapartum-related complications and infections, such as sepsis, meningitis, and pneumonia. According to estimates by WHO and the Maternal and Child Epidemiology Estimation group, 35% of all neonatal deaths in 2017 were due to complications associated with preterm birth; 24% of deaths were associated with Intrapartum events, such as birth asphyxia; 14% of deaths were due to sepsis or meningitis; and 11% were associated with congenital anomalies. Pre-eclampsia which is associated with preterm births accounts for 1 in 4 fetal deaths globally (Hodgins, 2015).

**2.2 Pre-eclampsia and eclampsia**

Hypertensive disorders such as pre-eclampsia and eclampsia, gestational hypertension, and chronic hypertension (ISSHP) are the second largest causes of MM globally. Preeclampsia is a disorder of pregnancy associated with new-onset hypertension (blood pressure > 140/90 mm Hg) and significant amount of proteinuria (≥300 mg in 24 h) in a healthy woman (Eiland et al., 2012), which occurs most often after 20weeks of gestation and frequently near term.

Although often accompanied by new-onset proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria (WHO 2019). Reliance on maternal symptoms may be occasionally problematic in clinical practice.

Preeclampsia can be classified as preeclampsia with or without severe features.

### 2.2.1 Diagnostic Criteria for Preeclampsia by WHO 2020

Blood pressure Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20weeks of gestation in a woman with a previously normal blood pressure

Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more indicate severe hypertension and should be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).

**and**

Proteinuria 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or Protein/creatinine ratio of 0.3 mg/dL or more or Dipstick reading of 2+ (used only if other quantitative methods not available)

**Or**

In the absence of proteinuria, a new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: Platelet count less than 100,000 3 109/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
- New-onset headache unresponsive to medicate and not accounted for by alternative diagnoses or visual symptoms.

### 2.2.2 Diagnosis of Preeclampsia with Severe Features by WHO 2020

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time).
- Thrombocytopenia (platelet count less than 100,000 /L
- Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

### 2.2.3 Pathophysiology or preeclampsia

Several mechanisms of disease have been proposed in preeclampsia including the following: chronic uteroplacental ischemia, immune maladaptation very low-density lipoprotein toxicity, genetic imprinting, increased trophoblast apoptosis or necrosis and an exaggerated maternal inflammatory response to deported trophoblast (Dekker GA et al 1998). More recent observations suggest a possible role for imbalances of angiogenic factors in the pathogenesis of preeclampsia (Wagner SJ et al 2011). It is possible that a combination of some of these purported mechanisms may be responsible for triggering the clinical spectrum of preeclampsia. For example, there is

clinical and experimental evidence suggesting that uteroplacental ischemia leads to increased circulating concentrations of anti angiogenic factors and angiogenic imbalances (Leung DN et al 2001).

**Vascular Changes:** Include hemoconcentration due to hypovolemia caused by the imbalances of various vasoactive agents, such as prostacyclin (vasodilator), thromboxane A2 (potent vasoconstrictor), nitric oxide (potent vasodilator), and endothelins (potent vasoconstrictors) resulting in intense vasospasm.

**Hematologic Changes:** Thrombocytopenia and hemolysis may occur and may reach severe levels as part of HELLP syndrome. Thrombocytopenia results from increased Platelet activation, aggregation, and consumption and is a marker of disease severity.

**Fetal Consequences:** As a result of impaired uteroplacental blood flow secondary to failure of physiologic transformation of the spiral arteries or placental vascular insults, or both. Abnormalities in the placental bed and subsequent failure of physiologic transformation of the spiral arteries in the first or early second trimester limit the blood flow to the uteroplacental unit. Additional mechanisms for chronic uteroplacental ischemia include placental vascular insults (Dekker GA et al 1998).

Among women with preeclampsia, clinical manifestations that follow from this uteroplacental ischemia include fetal growth restriction, oligohydramnios, placental abruption, and nonreassuring fetal status demonstrated on antepartum surveillance (Singal AB et al 2005). Consequently, fetuses of women with preeclampsia are at increased risk of spontaneous or indicated preterm delivery.

The condition occurs in 2-8% pregnancy worldwide and is one of the major causes of MM. PET is caused by disordered vascular development of the placenta which further widely spreads anti-angiogenic factors into the maternal circulation and causes a

systemic endothelial cell dysfunction and microangiopathy (Eiland et al., 2012). If untreated, the disease can progress to eclampsia; which is characterized by seizures in pregnant women (Al-jameil et al., 2014).

**2.3 Uric acid**

Uric acid (UA) is a heterocyclic organic compound with the formula C5H4N4O3 (7, 9-dihydro-1Hpurine-2, 6, 8(3H)-trione) and a molecular weight of 168 Daltons (Jin et al., 2012).

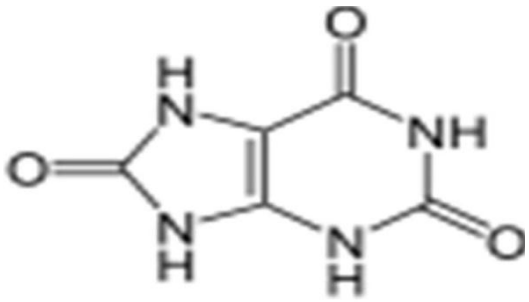



**Figure 2: Shows structure of uric acid**

Uric acid is synthesized mainly in the liver, intestines and the vascular endothelium as the end product of an exogenous pool of purines, and endogenously from damaged, dying and dead cells, whereby nucleic acids, adenine and guanine, are degraded into uric acid. UA is a marker of oxidative stress, tissue injury and renal dysfunction. It is the end product of purine metabolism and is synthesized by the enzyme xanthine oxidase/xanthine dehydrogenase (Ryu et al., 2019).

Many enzymes are involved in the conversion of the two purine nucleic acids, adenine and guanine, to uric acid. Initially, adenosine monophosphate (AMP) is converted to inosine by two different mechanisms; either first removing an amino group by deaminase to form inosine monophosphate (IMP) followed by dephosphorylation with nucleotidase to form inosine, or by first removing a phosphate group by nucleotidase to form adenosine followed by deamination to form inosine. Guanine monophosphate (GMP) is converted to guanosine by nucleotidase.

The nucleosides, inosine and guanosine, are further converted to purine base, hypoxanthine and guanine, respectively, by purine nucleoside phosphorylase (PNP). Hypoxanthine is then oxidized to form xanthine by xanthine oxidase, and guanine is deaminated to form xanthine by guanine deaminase. Xanthine dehydrogenase (XDH) is then converted to its oxidase form, xanthine oxidase (XO) through ischemia stimuli. XO then stimulates purine metabolism which results in Uric acid formation and production of free radical superoxide ($O_2^-$) which contributes to oxidative stress. XO is mostly found in liver and gut and is also a contributor of oxidative stress (Bainbridge and Roberts MD, 2012; Jin et al., 2012).

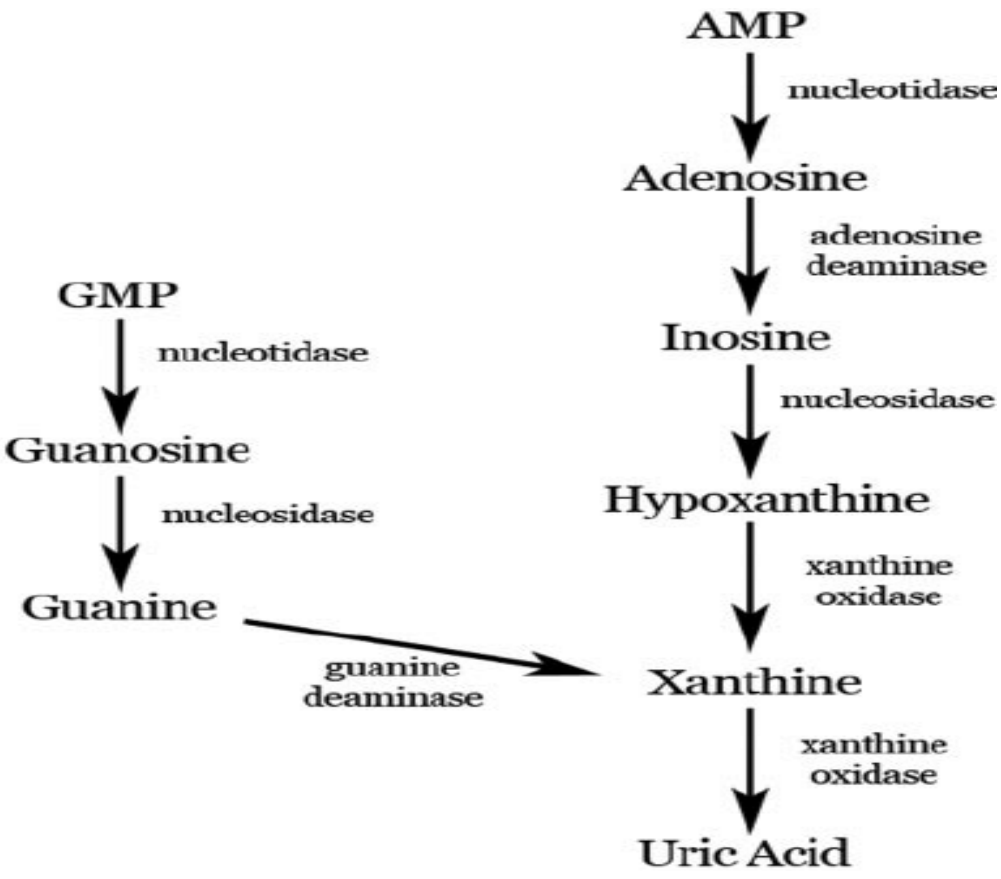



**Figure 3: Shows Enzymatic Formation of uric acid**

Humans unlike mammals do not have enzyme Uricase that breaks down uric acid into allantoin, a nontoxic product excreted by the kidney (Jin et al., 2012). Hence human excrete uric acid from the human body is through renal (Bainbridge and Roberts MD,

2012). The normal reference interval of uric acid in human blood is 1.5 to 5.0mg/dL in women and 2.5 to 6.0 mg/dL in men (Maiuolo et al., 2015). In healthy human beings, uric acid is minimally soluble and in its low state; usually maintained at (<6.0 mg/dL), it still possesses marginal dangerous biological functions. For instance, uric acid is associated with scavenging superoxide, hydroxyl radical and singlet oxygen; reduces nitrosylation of tyrosine residues on proteins by peroxynitrite; and maintains superoxide dismutase activity in some cases. Importantly, uric acid itself can become a pro-oxidant (urate radical) in a setting of compromised antioxidant availability, particularly reduced ascorbate availability. It also acts as a mediator of inflammation stimulating the production of monocyte chemoattractant protein-1, IL-1β, IL-6 and TNF-α (Bainbridge and Roberts MD, 2012).

The concentration of uric acid in human body is influenced by factors including; diet (i.e. high protein, and fructose), alcohol consumption, increased cell turnover, enzymatic defects in purine metabolism or altered kidney function (Maiuolo et al., 2015). Estrogen level also influences uric acid concentration which is high in men and post-menopausal women. In pregnant women, uric acid falls 25-35% during the early gestation. However, as pregnancy advances to late gestation, it rises to between (4-6 mg/dL), levels which are slightly higher than non-pregnant women (Bainbridge and Roberts MD, 2012).

Uric acid is elevated in pre-eclamptic pregnant women and was first noted in the 1800s. Since then, numerous studies have shown relationship between uric acid concentrations and severity of disease in pregnant women. Elevated uric acid which is manifested as reduced glomerular filtration rate, is detected as early as 10 weeks for women who go on to develop pre-eclampsia (Kamath et al., 2014). This is a time much earlier than the clinical presentation of pre-eclampsia. Reduced glomerular

filtration results in increased concentration of uric acid in the blood also referred to as hyperuricemia, which has historically been attributed to reduced renal clearance by the kidney in pre-eclampsia (Aswita et al., 2018). Increased uric acid from maternal or fetal or placental tissues, which is heightened by break down of tissues to raise substrate availability and increased XO activity results from placental ischemia-reperfusion injury, reduced antioxidant capacity and oxidative stress as it occurs in preeclampsia.

**2.4 Association between uric acid levels and severity of PE**

In a study by Sultana and colleagues in Bangladesh, which compared the mean levels of uric acid in subjects with normal blood pressure and preeclampsia, results showed that preeclampsia and its complications was associated with hyperuricemia. The mean serum uric acid concentration in cases and controls were 7.01±1.90 mg/dl and 4.55±1.63 mg/dl respectively and it was statistically significant (Sultana et al 2013).

Also, Gianni *et al* followed patients for a month after delivery and mentioned uric acid as a reliable predictor of preeclampsia in women with gestational hypertension. They indicated uric acid with cut-off of 309µm/l, as a predictor of severity of preeclampsia (Gianni et al 2018).

However, a study done by Chen *et al* stated that serum uric acid levels increased with the onset of clinical signs of preeclampsia, but it might not be a predictor of severity of preeclampsia and should not be considered as a predictive biomarker (Chen *et al* 2016). According to results, although preeclampsia might cause an increase in uric acid, the inverse association did not exist. Laughon *et al* found out that that the increase of uric acid in the first trimester of pregnancy was associated with severity of preeclampsia and its pregnancy complications during pregnancy complications were

related to hyperuricemia (Laughon et al 2019*)*. In a prospective case-control in Nigeria, the mean serum uric acid level was higher in the preeclamptic than in the normotensive controls (400.0±105.27 versus 256.31±67.18; p=0.001) compared to pre-eclamptic women with normal acid levels (Ngeri et al., 2022).

A systematic review study involving 6000 women have shown low evidence of using uric acid to predict severity of pre-eclampsia as indicated by the following pooled sensitivity (Se), specificity (Sp) and diagnostics odds (DOR); Se 0.74 (95%CI 0.71-0.77), Sp was 0.66 (95%CI 0.63-0.68), and DOR was 9.67 (95%CI 4.57- 20.47) respectively (Pecoraro and Trenti, 2020). The study concluded that there was no robust evidence currently existing to suggest that uric acid measurement is useful in predicting maternal and perinatal adverse outcomes (Pecoraro and Trenti, 2020).

**2.5 Association between uric acid levels and Maternal and Fetal outcomes**

The pathogenesis of preeclampsia which presents as dysfunctional placentation, systemic inflammation, and oxidative stress occurs due to failure of appropriate remodeling of the spiral arteries, resulting in higher resistance to placental blood flow and hypo perfusion of the placenta (Burton et al., 2019). This results in chronic placental ischemia and reduced blood flow to the developing fetus leading to adverse conditions to both the mother and fetus (Burton et al., 2019). For the mother, there is increased 2-to-4-fold risk of long-term hypertension, 1.5-fold risk of developing stroke, doubling risk of cardiovascular mortality and major adverse cardiovascular events, placenta abruption and oligohydramnios (Fox et al., 2019). For the fetus complications such as fetal hypoxia, intra-uterine growth restriction (IUGR), preterm birth (both spontaneous and iatrogenic), fetal distress, and fetal death in utero have been reported (Fox et al., 2019).

The occurrence of maternal and fetal outcomes in pre-eclamptic patients has been shown to increase with presence of serum uric acid. Studies have shown that raised serum level of uric acid with pre-eclampsia has significant relation with maternal complications namely: maternal death, increased number of emergency caesarian section and induction of labor, Premature rupture of membranes (PROM), Postpartum hemorrhage (PPH), Multiple dysfunction organ syndrome (MODS) and increased duration of hospitalization. Fetal complications such as low birth weight, preterm, still birth, intrauterine growth retardation; neonatal asphyxia and admission to NICU have been associated with high UA in PE mothers.

## 2.6 Fetal outcomes

### 2.6.1 Low birth weight

Low Birth Weight (LBW) is considered most important indicator of fetal and neonatal mortality and morbidity and is closely associated with other conditions such as inhibited growth and cognitive development and chronic diseases such as diabetes and cardiovascular diseases later in life (WHO, 2004). According to WHO, (2004) LBW is defined as weight at birth of less than 2500g. Preeclampsia is a dominant influence of birth weight and has been shown to increase cases of LBW and variation in birth weights compared to other maternal fetal conditions. In a prospective cohort study conducted by Nakimuli et al. (2020) found LBW of 2480g in babies born of mothers with pre-eclampsia diagnosed 28 weeks gestation. The study also reported a 7-10% variation in total birth weight caused by preeclampsia compared 0.05%-0.07% for other maternal fetal conditions combined. A significant variation in birth weight of between pre-eclampsia group and normotensive mothers of –547.5g to 239.5 g has been documented (Xiong et al., 2002).

Low birth weight cases in pre-eclampsia mothers have been shown to be notably high where high uric acid has been detected in pregnant women. A prospective observational study of women with preeclampsia showed that the optimal maternal serum uric acid threshold that predicted LBW at delivery was 6.35mg/dL (sensitivity, 0.58; specificity, 0.95) and concluded that serum acid was a predictor of low birth weight (Ryu et al., 2019). In a prospective study, conducted on 100 consecutive patients with preeclampsia/Eclampsia all having singleton pregnancy Kamath et al. (2014) found that 60 % of patients with uric acid levels > 5.5 mg/dl had birth weight < 2.5kg and 68% of them being small for Gestational Age. Mean birth weight of babies born from pre-eclampsia mothers with high serum 7.65±081 mg/dl was 2.07 kg, of which 24% babies had very low birth weight while 52% had low birth weight. While the mean birth weight of 2.82 kg was recorded to normal healthy mothers who had serum uric acid levels of 3.21±072 mg/dl (Meena et al., 2019).

A prospective cohort study in a tertiary referral centre in urban Uganda found that low mean birth-weight for pre-eclampsia cases which was2.48 kg (±0.81SD) compared to 3.06 kg (±0.46SD) for controls ($p < 0.001$) (Uwizeyimana et al., 2020). The study concluded that pre-eclampsia is the dominant predictor of birth-weight in low-resource settings and hence likely to heavily influence perinatal survival. A case-control study carried out in Federal Medical Centre, Umuahia, Nigeria found that women with elevated serum uric acid levels (>6 mg/dL) were found to be 4 times more likely to have severe preeclampsia ($P = 0.022$, OR=4.00, 95% CI = 1.225–13.056), and 3 times more likely to have lower birth weight (P=0.038, OR=3.400, 95% CI =1.073–10.775) than those with normal serum uric acid levels (Ugwuanyi et al., 2021).

Other studies have reported contrary results not all babies born from pre-eclampsia

women are of LBW. Akahori et al., (2012) found a strong negative correlation between serum uric acid levels and birth weights ($r = –0.59$; $p = 0.006$) normotensive pregnant women.

### 2.6.2 Preterm birth and labor

The WHO report defines preterm birth as babies born alive before 37 completed weeks of pregnancy (WHO, 2022). Preterm birth is classified into 3 categories based on gestational age: extremely preterm (less than 28 weeks) very preterm (28 to 32 weeks) moderate to late preterm (32 to 37 weeks) (WHO, 2022). Globally, 13.4 million infants were born preterm in 2022 and the condition is the second leading cause of child mortality after pneumonia accounting for 900,000 children deaths in 2019, while survivors face a lifetime of disability, including learning disabilities, visual and hearing problems (WHO, 2022).

Although half of the babies born preterm survive, the survival rates is higher in high income countries compared to low-income countries. For instance, half of the babies born at 24 weeks (4 months early) survive in high-income countries, but in low-income settings, half the babies born at 32 weeks (two months early) continue to die. This can be attributed to factors such as lack of feasible, cost-effective care, such as warmth, breastfeeding support, and basic care for infections and breathing difficulties (WHO, 2012).

The pathophysiology that triggers preterm births is complex and is still unknown despite existing studies which have been done to understand the etiology and complications related to preterm births. Etiology and complications of preterm births include; multiple gestation Mheen et al. (2014); Olusanya, (2011), antepartum hemorrhage or bleeding during pregnancy Bhandari et al., (2013; Klinger, (2020) and

diabetes (Crump et al., 2020; Li et al., 2014). Hypertensive disorders such as pre-eclampsia largely contribute to cause preterm births. Connealy et al. (2014) reported 23% preterm births before 37 weeks gestation among pre-eclampsia women. Davies et al. (2016) in a population case-controlled study also found a strong association between preterm and preeclampsia and concluded that the condition was a potential targeting in reducing preterm deaths.

The severity of preterm birth deliveries in pre-eclampsia mothers has been shown to increase with high levels of uric acid and some studies have been documented. A diagnostic test and historical cohort study conducted by prospective cross-sectional data collection on pregnant women with pre-eclampsia/eclampsia showed that high uric acid level (≥393 μmol/L) resulted in increased risk of preterm birth (OR 6.367, 95% CI 3.009–13.084) (Le et al., 2019). In cross-sectional study, with 160 singleton preeclampsia women at more than 28 weeks of gestational age, Asgharnia et al., (2017) found significantly high level of uric acid in pre-eclampsia mothers which led to preterm delivery (OR: 1.54, 95% CI: 1.15-2) and concluded that serum uric acid can be used as a measurement marker in severe preeclampsia.

A prospective observational study of women with preeclampsia showed that serum uric acid levels were significantly higher in those who experienced preterm labor 6.2±1.7; compared to full-term, 5.1±1.3 and concluded that uric acid can be used to predict pre-eclampsia in women with low birth weight (Ryu et al., 2019). In a prospective study, conducted on 100 consecutive patients with preeclampsia/Eclampsia all having singleton pregnancy (Kamath et al. (2014) found that 60 % of patients with uric acid levels > 5.5 mg/dl had preterm delivery and concluded that serial monitoring of serum Uric acid level can help reduce maternal

and fetal outcomes in pre-eclampsia mothers.

In a cross-sectional comparative study conducted on 100 cases of pre-eclampsia mothers and 100 cases of normal healthy mothers (control group) of age group 20-40 and gestational age ≥28 weeks found that mean serum uric acid levels in preeclampsia was 3.65±081 mg/dl compared to and 3.21±072 mg/dl in control group (Meena et al., 2019). The study concluded that there was no positive association between serum uric acid levels and severity of pre-eclampsia on maternal and fetal outcomes. Patients with preeclampsia, serum uric acid level 6.35mg/dL (sensitivity, 0.58; specificity, 0.95) were associated with preterm labor (P=.027) (Ryu et al., 2019). The study concluded that women with preeclampsia, maternal serum uric acid level are an important parameter for predicting preterm labor. A cross-sectional study showed that preterm birth of 46% was reported in pre-eclamptic women with mean of serum uric acid concentration was 7.09+0.60 mg/d and 54% in normal uric acid (Lakhan et al., 2020). The study concluded that Intrauterine growth restriction and preterm birth are common features of obstetrical and perinatal challenge. Patients having serum uric acid > 6.0 mg/dl showed mild pre-eclampsia 31 (15.5%) to moderate preeclampsia 52 (26%) which was associated still birth in 96 (48%) patients (Mumtaz et al., 2022).

Cases of preterm births have been found to be high and associated with neonatal deaths within the African continent. In Ghana, the percentage of preterm births was 3.2%, in Tanzania 4.9% and 7.4% in Zambia which contributed to high preterm deaths of 40% in Sub-Saharan Africa, in pre-eclamptic mothers with high uric acid (Nisar and Yoshida, 2022).

### 2.6.3 Neonatal Asphyxia

Neonatal asphyxia is an acute respiratory failure, that is, a rapid decrease in alveolar ventilation at birth or shortly after birth. This condition is accompanied by hypoxia, hyper apnea, and ends with acidosis. Long-standing asphyxia can cause brain damage and death (Kusumaningrum et al., 2019). Neonatal asphyxia is as a result of low Apgar scores (Aslam et al., 2014). According to WHO estimates, neonatal asphyxia accounts for 38% of child death at birth (Bryce et al., 2005). New born babies who have asphyxia have a high chance of developing severe consequences such as epilepsy, cerebral palsy and developmental delay. Among the risk factors to neonatal asphyxia are severe eclampsia and pre-eclampsia (Aslam et al., 2014). A cross-sectional study conducted by (Gabkika et al. (2018) found pre-eclampsia among the main etiologies of birth asphyxia accounting 10.2% of cases. Kusumaningrum et al. (2019) also showed that the risk of asphyxia increased with pre-eclampsia.

Some researchers have found the risk of birth asphyxia in pre-eclampsia with high serum uric acid levels in pregnant mothers and some found no associaton and supporting research is available. In a prospective case control study, high serum uric acid of 405.6±995 μmol/L in participants with pre-eclampsia was associated significantly with birth asphyxia (Obagah et al., 2020). In another case control study, Nesa et al. (2019) found that the serum uric acid (SUA) was 7.03±1.89 mg/dl and 4.49±1.72 mg/dl and resulted in 30% and 12% birth asphyxia cases in preeclampsia and normotensive respectively. The study also indicated low percentage in APGAR scores in pre- eclampsia than normotensive women: 30% and 45%; 82% and 90% for 1 minute and 5 minute APGAR score ≥7 respectively (Nesa et al., 2019).

Lin et al, (2018) reported serum uric acid levels of was 340.0 ± 119.6 μmol/L in women with hypertensive disorders which was highly associated with birth asphyxia compared to Serum uric acid of 295.8 ± 81.7 μmol/L in normal women. Also, high uric acid level (≥393 μmol/L) resulted in increased risk of low Apgar scores (OR 5.514, 95% CI 1.877–16.198) (Le et al., 2019). In other studies serum uric acid has been used as an important marker in predicting birth asphyxia isolating pre-eclampsia cases (Baranala and Kumar, 2020; Bhongir et al., 2015; Kumar et al., 2017). An Institution based unmatched case control study was conducted among newborn live births in public hospitals of Gamo & Gofa zones and the findings showed that the odds of perinatal asphyxia were nearly three times higher 2.95 (0.60–14.34) among those who developed preeclampsia or eclampsia and had high UA compared to the control group (Lemma et al., 2022). A cross-sectional study in a hospital in Northern Ethiopia showed that high UA in preeclampsia (AOR = 7:94, 95% CI: 2.22-28.37, P = 0:001) was an important determinant factors for birth asphyxia (Gebregziabher et al., 2020).

There are incidences where birth asphyxia has not been associated with pre-eclampsia. In a prospective case control study, high uric acid 405.6±995 μmol/L in preeclamptic women was not statistically associated with the occurrence of birth asphyxia (p=0.56) (Obagah et al., 2020). Nisar and Yoshida, (2022) in a descriptive cross-sectional study found no significant differences (P > 0.05) between the mothers in the asphyxia group and non-asphyxia group on the following conditions; pre-eclampsia with high UA, HIV positive sero status, and Cephalo Pelvic Disproportion (CPD), suggesting that these were not associative factors for birth asphyxia. In a study done by Meshesha et al., 2020 found Low birth weight (AOR: 8.94, 95%CI: 4.08, 19.56), born at health centers (AOR: 7.36, 95% CI: 2.44, 22.13), instrumental delivery

(AOR: 3.03, 95%CI: 1.41, 6.49), and prolonged labor (AOR: 2.00, 95%CI: 1.20, 3.36) were significant determinants of birth asphyxia in 20% of mothers with pre-eclampsia and not high uric acid (Meshesha et al., 2020).

In an analytic observational study with a case control design conducted in Nganjuk Hospital, East Java, the risk of asphyxia was shown to increase with pre-eclampsia with high UA than in the controls with normal UA (OR= 3.74; 95% CI= 12.54 to 141.05; p <0.001) (Kusumaningrum et al., 2019). In a prospective case-control in Nigeria, the mean serum uric acid level was higher in the preeclamptic than in the normotensive controls (400.0±105.27 versus 256.31±67.18; p=0.001) compared to pre-eclamptic women with normal acid levels (Ngeri et al., 2022). This high serum levels were pre-eclamptic women were not associated with higher incidence of birth asphyxia (p=0.002) (Ngeri et al., 2022).

### 2.6.4 Intrauterine Growth Retardation and Small for Gestation age

Intrauterine growth retardation (IUGR) and Small Gestation Age (SGA) are used interchangeable to describe almost the same condition. IUGR is the failure of the fetus to achieve his/her intrinsic growth potential, due to anatomical and/or functional disorders and diseases in the feto–placental–maternal unit (Murki and Sharma, 2014). It is the second leading cause of +-perinatal mortality after preterm births (Tesfa et al., 2020). IUGR is characterized as; symmetrical if weight, length, and head circumference are low, usually indicative of a process originating early in pregnancy and asymmetrical when brain sparing takes place and the head circumference is within normal limits, indicative of a process occurring as gestation advances (Briana and Malamitsi-puchner, 2009). IUGR is associated with inadequate trophoblast invasion, an inadequate transformation of spiral arteries, followed by respective

changes in the blood flow of the uterine arteries, alterations of the umbilical blood flow, and restrictions of fetal growth (Huppertz, 2008). IUGR affects approximately 24% that is 30 million babies globally every year (Tesfa et al., 2020).

IUGR is associated with pre-eclampsia and elevated uric acid and studied investigating such cases exists. In a prospective study with primiparous women having a singleton pregnancy, it was found that there was a high association between maternal serum uric acid and the chance of giving birth to a small-for-gestational-age infant, with the unadjusted odds ratio of 1.7 (95% CI: 1.4 to 2.2; P=0.001), and 1.6 (95% CI: 1.1 to 2.4; P=0.02) after adjustment (Bellomo et al., 2011).

There was a high occurrence of IUGR 20 (40.0) cases in pre-eclampsia mothers who had high SUA of 7.19±0.62 mg/dl compared to IUGR cases of 4 (8.0) in normal mothers with SUA of 4.83±0.73 mg/dl (Mahjabeen et al., 2019). Also, high uric acid level (≥393 μmol/L) resulted in increased risk of intrauterine growth restriction (OR 7.188, 95% CI 3.592–14.382) (Le et al., 2019). Additionally, in an observational prospective approach, uric acid increased after the 30th week of gestation and was found to be higher more than 1.5 times the normal towards the end of the gestation period and was associated with IUGR (Corominas et al., 2022). The study showed that uric acid at a cut-off point >1.5 times increase had a very low positive predictive value, but a high negative predictive value of 99.5% for preeclampsia (Corominas et al., 2022). The study thus concluded that uric acid level below 1.5 values may be a helpful parameter with a strong exclusion value and high sensitivity for those women who are not expected to develop preeclampsia. In a cohort study, mean serum uric acid level was 7.416±1.04 pre-eclamptic group compared to 4.202±0.61 in control group. The high uric acid led to 93.3% cases of intrauterine growth restriction compared to 60% in group in the control group (P=0.002) (RRR=55.5%) (Nadeem et

al., 2022). The study also showed low birth weight was 70% in group pre-eclamptic group compared to 10% in group control group (P=0.000) (Nadeem et al., 2022). The study concluded that pregnancies with pre-eclampsia and raised serum uric acid levels result in adverse fetal outcome.

In a prospective case control study involving 200 (100 pre-eclampsia and 100 non-pre-eclampsia mothers) Obagah et al. (2020) found that 20.0% of babies born from pre-eclampsia mothers with SUA level of (405.6±995 μmol/L) had intrauterine growth retardation. In the same study no babies born from normal mothers with SUA levels of 232.7±26.3 μmol/L experienced IUGR (Obagah et al., 2020). Other studies have shown less linkage of uric acid in pregnant women and SGA or IUGR. In a systematic review study conducted on 3913 women, Thangaratinam et al., (2006), found serum uric acid of 350-mmol/l threshold to be a poor predictor of SGA, i.e the pooled LRs were 1.3 (95% CI 1.1–1.7) and 0.60 (95% CI 0.43–0.83) for positive and negative results, respectively. In a retrospective cohort study of 249 singleton pregnant women Wu et al. (2012) found that adverse maternal effects including intrauterine growth restriction (<3rd percentile) were not high 50.1% in pre-eclampsia mothers with serum uric acid levels of 5.06 ± 0.78mg/dl compared to IUGR cases of 749.9% in normal mothers with SUA levels of 4.59 ± 1.01.

### 2.6.5 Still birth

The recommended definition for still birth is a baby born with no signs of life after a given threshold, usually related to the gestational age (mostly or after 28 weeks' gestation) or weight of the baby (UNICEF, WHO, United Nations, World Bank, 2020). Globally, nearly 2 million babies are stillborn with Sub Saharan Africa and Southern Asia accounting for 84% of still births. Still births are preventable and the

Every Newborn Action Plan (ENAP) to end preventable deaths has a set stillbirth target of 12 per 1000 births or less by 2030. Hence it is important to understand the cause and initiate interventions that improve the health of mothers and their newborns along the continuum of care.

Hypertensive disorders such as pre-eclampsia are associated with increased risk of still births. The prevalence of still births increases with rising serum uric acid levels in pre-eclampsia women. Stillbirth at 7% out of the 126 cases of pregnancy occurred with serum uric acid level ≥5.5mg/dl in mothers with incidence of pre-eclampsia (Singh et al., 2014).

High cases of still birth 24 (35.82) occurred in pre-eclampsia patients who had serum uric acid levels > 6mg% compared to non-pre-eclampsia patients with SUA levels < 6mg% which were 10 (30.30) (Haider et al., 2019). In another prospective clinical observational study carried out on women with gestational age of 28-40 weeks, the mean serum uric acid and fetal death was 6.37 mg/dl and 22% compared to 3.6 mg/d and 0% for pregnant women with severe preeclampsia and normotensive respectively (Nair and Savitha, 2017).

Some studies have indicated no relationship between uric acid and stillbirths. In a systematic review study conducted on 3913 women, Thangaratinam et al., (2016), found serum uric acid of 350-mmol/l threshold to be a poor predictor of stillbirths and neonatal deaths indicated by the LRs of 1.5 (95% CI 0.91–2.6) and 0.51 (95% CI 0.20–1.3) respectively. Le et al., (2019) has also shown no relationship between uric acid and fetal death, that is (OR 1.803, 95% CI 0.355–9.168). The cases of still birth were high that is 7 which were associated with women with hypertensive disorders with serum uric acid level >6 mg/dL compared to 2 cases in the control group with

uric acid level <6 gm/dL (Ahmed and Dewan, 2017). The study concluded that high uric acid in blood in patient with hypertensive disorders in pregnancy is a risk factor for perinatal complications such as still birth. Patients having serum uric acid > 6.0 mg/dl showed mild pre-eclampsia 31 (15.5%) to moderate preeclampsia 52 (26%) which was associated still birth in 33 (16.5%) of the patients (Mumtaz et al., 2022).

### 2.6.6 Admission to NICU (Neonatal Intensive Care Unit)

Neonatal Intensive Care (NICU) is a care that provides life support to new born babies. The risk factors associated with increased odds of admission of term infants to the NICU include; operative method of birth, elective delivery before 39 weeks either vaginally or by cesarean section, maternal diabetes and hypertension, multiple pregnancy (twins, triplets, or more), drug or alcohol use, premature rupture of membranes, low socioeconomic status among others (Al-wassia and Saber, 2017). Approximately 54.5% of the live babies born of pre-eclamptic mothers were admitted to NICU due to a combination of prematurity, low birth weight, and respiratory distress syndrome (RDS), and 18.5% were due to low Apgar scores (Ngwenya, 2017). Belay et al. (2020) also found that the 36.6% of babies born from women with hypertensive disorders required admission to NICU.

Other studies have shown cases requiring NICU on the rise and are precipitated by pre-eclampsia and serum uric acid. Women with high levels of uric acid serum had more than two folds increased risk for their neonate being admitted to Neonatal Intensive Care Unit OR (2.4) (Saad et al., 2011). Intensive care unit (NICU) referral was high (60%) in pre-eclamptic conditions with mean serum uric acid level was 7.19±0.62 mg/dl compared NICU of 20% reported in normal women who serum uric acid of 4.83±0.73 mg/dl (Mahjabeen et al., 2019). In another study the mean serum

uric acid levels in preeclampsia was 7.65±081 mg/dl resulted in admission to NICU at 34% of babies compared to 8% observed in normal women who had SUA levels of 3.21±072 mg/dl (Meena et al., 2019). There was a positive but a positive association between uric acid levels and admission to neonatal unit ($p < 0.001$) (Gowri & Al-Zakwani, 2010).

Yet other studies have found no relationship between elevated uric acid and NICU. Uric acid levels in women had no significant effect with (NICU) (Asgharnia et al., 2017). The study attributed NICU admission to other factors such as increase in hemoglobin, aspartate aminotransferase (AST) and history of hypertension increased risk of hospitalization in NICU; that is 1 mg/dl increase in hemoglobin and AST in pregnant women with preeclampsia, 1.6- and 1.022-fold increase in the risk of hospitalization in NICU was noted, respectively. Admission to NICU has also been due to other complications such as birth asphyxia Kumar et al. (2017), and micro albuminuria (Chawla and Malik, 2018).

### 2.7 Maternal outcomes

Maternal outcomes in pre-eclamptic women with Serum Uric acid levels include the following; maternal death, PROM, Increased cases of emergency caesarian section, increased cases of induction of labor PPH, organ failure and increased duration of hospitalization.

#### 2.7.1 Maternal death

Maternal death or maternal mortality is defined by the World Health Organization (WHO) as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause

related to or aggravated by the pregnancy or its management but not from accidental or incidental causes (WHO 2016). Causes of MM have widely been studied and documented and they range from indirect and direct (Brown et al., 2013; Lumbiganon et al., 2014; Sageer et al., 2019; Say et al., 2014; Yakasai and Gaya, 2011; Yego et al., 2014). Indirect causes account for 27.5% and are aggravated by conditions related to diseases such as malaria, heart disease, diabetes, HIV and anemia among others (Lumbiganon et al., 2014). Direct causes attributed to obstetric account for 73% of the deaths and are caused by conditions such as hemorrhage-27.1%, hypertensive disorders (pre-eclampsia and eclampsia)-14.0%, Sepsis-10.7%, Abortive outcomes-7.9% and embolism and other conditions-12.8% (Black et al., 2016).

Hypertensive disorders which consist of pre-eclampsia and eclampsia are the second causes of maternal death which occur highly in women with elevated serum uric acid. A study done by Kumar at el showed that there was high maternal mortality 62.5% in pregnant women with pre-eclamptic conditions who had serum uric acid of 6.8 ± 2.72 mg/dl compared to 0% death in the control group i.e. women with no pre-eclamptic conditions who had serum uric acid 4.42 ± 1.42 mg/dl (Kumar and Singh, 2019). Pacarada et al., (2016) reported a case of a pregnant woman with severe preeclampsia at 29-week gestation with the following clinically presentation; Pericardial effusion, pulmonary edema, Respiratory insufficiency, high uric acid which led to death after 10 days of cesarean delivery postpartum. Hemolysis elevated liver enzymes and low platelet syndrome which was presented in a case of severe PET in mothers with raised UA resulted in maternal death (Ngwenya, 2017). Maternal mortality at 2.2% was recorded in pre-eclamptic mothers with SUA levels of 5.0±1.74 mg/dl compared to 0% cases in normal mothers with 2.66±0.39 mg/dl (Saldanha et al., 2018). Andrews et al., (2016) also found maternal death occurred in 09 cases (2.8%) in pre-eclamptic

mothers with high SUA. Maternal death was a complication in 4 (4.65%) cases with PET and high uric acid levels >5.5mg/dl. The study concluded that elevated Serum uric acid levels might be used as a biochemical indicator of maternal and neonatal morbidity and mortality in Preeclampsia and Eclampsia (Jampana et al., 2022). A cross-sectional study done in two tertiary hospitals in Cameroon showed that the maternal mortality of 05(5.1%) in pregnancy induced hypertensive (PIH) cases and out this 04(80%) had uric acid level > 5.5mg/dl (Essiben et al., 2016). In the same study, Perinatal mortality was observed in 25 (25.1%) cases, out of these 19(76%) were stillbirths and 06(24%) were neonatal deaths. Out of the 25 perinatal deaths 18(72%) had uric acid level >5.5mg/dl. The study concluded that serum uric acid level could be used as a biochemical indicator of preeclampsia/eclampsia and its complications (Essiben et al., 2016).

### 2.7.2 Multiple dysfunction organ syndromes (MODS)

The Multiple Organ Dysfunction Syndrome (MODS) can be defined as the development of potentially reversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission, and arising in the wake of a potentially life-threatening physiologic insult (Curran, 2002). Causes of MODS include; postpartum hemorrhage, severe preeclampsia or eclampsia, pregnancy with hepatitis, pregnancy with heart disease, ectopic pregnancy.

Preeclampsia causes maternal organ and system dysfunction; like hematological, hepatic dysfunction, neurological disorders or renal involvement. High incidences of hemolysis, neurological complications, frequent occurrence of severe cardiorespiratory and hematological complications have been found in patients with preeclampsia (Anna et al., 2019). Pacarada et al., (2016) reported a case of a pregnant woman with severe preeclampsia at 29-week gestation with the following clinically

presentation; Pericardial effusion, pulmonary edema, Respiratory insufficiency. Ngwenya, (2017) showed severe PE incidence of 1.3% that is 121 cases out of 9086 deliveries that were recorded which clinically presented as hemolysis elevated liver enzymes, low platelet syndrome. High uric acid level in patients with pregnancy-induced hypertension was a risk factor for several maternal complications like postpartum hemorrhage (12 versus 7 cases), postpartum eclampsia (7 versus 3 cases), abruptio-placentae (6 versus 2), HELLP syndrome (2 versus 0) and pulmonary edema (3 versus 0). In a prospective case-control in Nigeria, the mean serum uric acid level was higher in the preeclamptic than in the normotensive controls (400.0±105.27 versus 256.31±67.18; p=0.001) compared to pre-eclamptic women with normal acid levels. This high serum levels were pre-eclamptic women were associated with higher incidence of acute kidney injury (p=0.005) (Ngeri et al., 2022).

Studies have also shown that MODS in pre-eclamptic conditions are exacerbated by elevated uric acid in pregnant women. Uric acid promotes endothelial dysfunction leading severe cases such as vascular disease, HELLP, renal disease among others. Asgharnia et al. (2017) found that 1 mg/dl increase in blood uric acid level induced 1.74 fold increase in the risk of hepatic dysfunction (OR: 1.74, 95% CI: 1.12-2.72) and concluded that higher level of uric acid in severe preeclampsia can result in more complications such as hepatic dysfunction and hence HELLP syndrome. Elevated Serum uric acid levels (382 ± 78 Umol/L) in women with gestational hypertension led to HELLP syndrome. These findings were contrary to Williams and Galerneau, (2002) that women with SUA levels 330 ± 80 umol/L did not have HELLP syndrome.

**2.8 Factors associated with in pre-eclampsia in pregnant women with high uric acid.**

Risk factors linked with pre-eclampsia are a range of conditions whose strength of associations is quantified using risk ratios or odd ratios. The factors are includes: family history of preeclampsia, previous history of PE, obesity, prim parity, pre-existing hypertension, Diabetes, renal disease, age, ant phospholipid antibodies, multiple gestation (Kenny and Mccarthy, 2015; You et al., 2018).

In a prospective cross section study conducted in Hue hospital in Vietnam, (2018) on Maternal serum uric acid concentration and pregnancy outcomes in women with pre-eclampsia/eclampsia concluded that there was no association between uric acid level and maternal factors such as age, parity, or delivery method. The only associated factor was gestation less than 34 weeks (OR 5.188, 95% CI 2.790–9.649; $P<0.001$) (Tamet al. 2020).

A study done on association of urid acid with progression to preeclampsia and development of adverse pregnant outcome in Saint Justine Hospital, Montreal Canada concluded that; previous history of pre- eclampsia,a high diastolic blood pressure, gestational diabetes mellitus and caesarean section were associated with poor prinatal and maternal outcome (Yuquan et al 2012).

A meta-analysis study conducted in Sub-Saharan countries using electronic database MEDLINE, EMBASE, PubMed, CINAHL published in English from January 2000 to May 2020 also identified the following factors associated with pre-eclampsia in pregnant women with high uric acid. These factors include; primigravida , previous history of maternal preeclampsia/eclampsia, family history of preeclampsia/eclampsia, high maternal body mass index, chronic hypertension, Gestational Diabetes and lack of antenatal care visits (Wagnew et al., 2020). The

same study concluded that the most maternal factors associated with uric acid in preclamptic mothers were; history of preeclampsia/eclampsia (either themselves or family members), primigravida, obesity and overweigh, living with chronic disease during pregnancy, women older than 35years and absence from ANC visits (Wagnew et al., 2020).

In a study conducted in Mpilo Central Hospital, Bulawayo, Zimbabwe, Ngwenya et al. (2019) concluded that gestation age and platelet count were significantly associated with adverse maternal outcomes in pre-eclamptic mothers with hyperurecemia. Mothers with platelet counts of 0–49 × 109/l were 46 times more likely to be associated with adverse maternal outcome compared to mothers with normal counts of more than 150 × 109/l.

A study carried out in a Mettu Karl referral hospital in Ethiopia found that factors associated with pre-eclampsia and poor maternal and perinatal outcomes were; age less than 20years,attending ANC fewer times, current multiple pregnancy and history of diabetes mellitus (Belay and Wudad, 2019).

Furthermore, the incidence of pre-eclampsia and distribution of risk factors of pre-eclampsia were identified in a study done in Paropakar Maternity and Women's Hospital, Kathmandu, Nepal, concluded that women older than 35 years were more at risk of PE and poor pregnant outcome (Adjusted Odds Ratio, AOR)= 3.27; (Confidence Interval, in comparison to mothers aged 20–24 years. The same study revealed that primigravida women, women with gestational age less than 37 weeks, twins pregnancy, chronic hypertension urinary tract infection, and gestational diabetes were at increased risk of developing severe PE and its complications (Das et al., 2019).

Nathan et al. (2018) in a hospital level facility observed that young maternal age (AUROC = 0.76, 95% confidence interval (CI) = 0.71-0.80) and low Body Mass Index BMI (AUROC 0.65, 95% CI = 0.59-0.69) were significant predictors of eclampsia and pregnant outcome. The same study concluded that teenage mothers and those with low BMI were at highest risk of preeclampsia and coplications. , Guerrier et al. (2013) with a greater risk of severe preeclampsia/eclampsia concluded that personal history of preeclampsia (odds ratio [OR] = 21.5; P , 0.001), personal history of preexisting hypertension (OR = 10.5; P , 0.001), primigravida (OR = 2.5; P = 0.001), occupation as housewife (OR = 1.9; P = 0.008), and fewer than four antenatal care visits (OR = 1.6; P = 0.02) were risk factors for developing PE complications.

A cross-sectional study conducted in Zanzibar found factors related to severe preeclampsia to include; maternal age group of 15–20 years, pregnancy from a new partner, family history of high blood pressure, diabetes prior to conception), having high blood pressure in a previous pregnancy, gestation less than 37 weeks and multiple gestation (Machano and Joho, 2020).

In a case control study carried out in at Nairobi County Hospital, pre-eclampsia and it's complications were significantly linked with personal history of hypertension, Nulliparity , primigravida, advanced maternal age 35-49 years), and the occurrence of preeclampsia/eclampsia in the previous pregnancy (Logan et al., 2020).

There are studies that have shown contradictory findings on risk factors associated with pre-eclampsia. Although high uric acid levels are associated with pre-eclampsia, in young women below 20 years (OR=4.2; IC= [1.2-15]; P =0.002), other factors such as marital status, parity, educational level, gestational age at time of diagnosis, the timing with respect to labor, and blood pressure values have not been shown to

influence significantly the risk of developing eclampsia (Essiben et al., 2016).

### 2.8.1 Modes of delivery

Modes of delivery refer to either the natural delivery (spontaneous vertex) or a delivery by surgical intervention (caesarean). Spontaneous vertex delivery (SVD) is the birth of babies through the vagina while Caesarean section delivery is a surgical procedure in which one or more incisions are made through a mother's abdomen and uterus to deliver one or more babies (Mbombo et al., 2018). Although SVD is preferred than CS and the WHO has recommended that delivery through CS should be limited to 10-15% of deliveries worldwide, current trends show the number of CS are on the increase (Vega, 2015; WHO, 2015). This has been attributed to factors such as; financial incentives, lack of regulations, maternal requests Tadevosyan et al. (2019); maternal age, parity, diseases like HDP, caesarean indicative motive and economic status (Vega, 2015). High CS cases and high labour induced delivery have also been observed in pre-eclamptic women with high serum uric acid. In a retrospective study conducted on 94 women with pre-eclampsia Gowri and Al-Zakwani, (2010) found that cesarean delivery was significantly high, that is 33% in patients with PET and elevated uric acid (>0.35 mmol) irrespective of whether they were preterm or term compared to 12% in normal mothers. Induced of labour followed by lower segment caesarean section was the most common mode of delivery in hypertensive cases with high serum acid levels, compared to normotensive mothers where the majority had spontaneous onset of labour and delivered vaginally (Kumar and Singh, 2019).

Higher requirement of labour induction and caesarean section was seen in severe PET with raised UA than in normal women (N et al., 2019). Also, the overall rates of caesarean delivery were significantly higher among women with preeclampsia with 6.738±1.68 mg/dl compared to control group ($p<0.0001$) who had SUA levels of 4.22 ± 0.5 mg/dl (Ah et al., 2016). In another case control study, caesarean section rate was significantly higher (65%) among pre-eclampsia women with high SUA of 6.38 mg/dl than in normal mothers (30%) with SUA levels of 5.05 mg/dl (Saad et al., 2011). Additionally, Le et al., (2019) observed that there more cases of CS deliveries (100) compared to vaginal delivery cases (31) in pre-eclamptic mothers who had high SUA levels of Uric acid ≥393 μmol/L.

On the other hand, some studies have shown no association between uric acid and CS deliveries. For example Thangaratinam et al., (2006) found no association between uric acid and CS as shown in the following likelihood ratio positive and negative LRs; 2.4 (95% CI 1.3–4.7) and 0.39 (95% CI 0.20– 0.76) for CS. A retrospective study found that hyperuricemia preeclamptic mothers were not associated with higher probability of delivery by caesarean section (33% versus 32%; $p = 0.56$). The study concluded that hyperuricemia in preeclamptic patients was no associated with higher probability of cesarean delivery (Gowri and Al-zakwani, 2010).

# CHAPTER THREE

## 3.0 METHODOLOGY

### 3.1 Study Design

The study used a cross-section comparative study that was carried out in postpartum preeclamptic women from January 2022 to December 2022 at Moi teaching and referral hospital in Eldoret Kenya.

### 3.2 Study Area

The study was done at Moi Teaching and Referral Hospital (MTRH), the second-largest referral Hospital in Kenya located in the western part of the country, at Eldoret, in Uasin Gishu County.

The hospital doubles as the teaching hospital for Moi University School of Medicine. It has a vast catchment area, serving the populations from Western, Nyanza, and Rift valley regions; hence a complex array and mix of cases are seen in this facility. On average, 1000-1400 deliveries are conducted per month at the facility.(MTRH statistics, 2022).

The hospital has a well-equipped obstetric unit that has one antenatal ward (ANW), one labor ward (LW), one postnatal ward (PNW) and two maternity theatres. Labor ward (LW) has a bed capacity of 18 beds. A pregnant woman reports to labor ward where a team of two residents in obstetrics and gynecology and midwives attend to her. A specialist on call assists in giving guidance. In labor ward we have an acute room where we manage very sick patients including those with pre-eclampsia. On average we see 40 pregnant mothers per day and four mothers with pre-eclampsia and eclampsia. The PNW has a bed capacity of 40 beds and acute room where we manage very sick patients including those with severe preeclampsia.

On average, 1000-1200 deliveries were conducted per month at the facility (MTRH statistics, 2020) translating to approximately 40 pregnant mothers per day of whom three to four (10%) women have pre-eclampsia or eclampsia.

The hospital has a standard protocol for managing preeclampsia. The patients were enrolled from postnatal wards within the reproductive unit of the hospital

### 3.3 Study population

The study population was postpartum women diagnosed with preeclampsia at Riley Mother and Baby Hospital (RMBH) at Moi Teaching and Referral Hospital from January 2022 to December 2022. Those aged less than 18 years old were included in the study, but both the parent/guardian and patient were required to sign consent and assent forms, respectively.

### 3.4 Eligibility criteria

#### 3.4.1. Inclusion criteria

1. All postpartum women admitted at RMBH post natal ward and diagnosed with pre-eclampsia defined according to ACOG Practice Bulletin (2018), as BP ≥140/90 mm Hg associated with proteinuria (300mg or more in 24 i.e. hours, protein/creatinine ratio of 0.3 or dipstick reading of 2+) or associated thrombocytopenia (platelets (high blood pressure ≥140/90 mmHg, pulmonary oedema or Impaired liver function or Eclampsia (associated with fits).
2. All the postpartum women admitted at post natal ward with serum uric acid lab results taken at admission in labor ward or 24 hours before delivery.

### 3.4.2 Exclusion criteria

1. Postpartum women with overt or gestational diabetes, chronic hypertension, nephropathy, chronic renal failure, hepatic dysfunction, gout or cancer were excluded.
2. Postpartum women with obstetric complication e.g. breech presentation, multiple pregnancies, fetal and placental malformations.
3. Postpartum women with a history of smoking, alcohol or other substance abuse.
4. All postpartum women with PET admitted at post natal ward without the SUA lab results

### 3.4.3 Exposed group definition and recruitment

- An exposed group was defined as a Postpartum woman admitted MTRH post natal ward having been diagnosed of preeclampsia and had elevated uric acid.

### 3.4.4 Non-Exposed group definition and recruitment

- Non-Exposed group was defined as a postpartum women admitted at MTRH postnatal ward having been diagnosed of preeclampsia and had normal uric acid.

## 3.5 Sample size

The aim of the study was to compare maternal and perinatal outcomes between those with elevated serum uric acid and those with normal serum uric acid levels. A study done by Le, et al,. (2019) found the proportion of neonates with APGAR <7 among women with elevated SUA to be 18.3% compared to 3.8% among those with normal SUA. The sample size was estimated using sample size calculation formula for

comparing two proportions as described by Fleiss, (1981).

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

Where;

n = minimum sample size for one group (exposed)

r = 2:1 ratio (unexposed to exposed)

$\bar{p}$ = pooled prevalence

$Z_{\beta}$ = critical value corresponding to 80% power

$Z_{\frac{\alpha}{2}}$ = critical value corresponding to 0.05 type I error

$p_1$ = (18.3%) proportion of neonates with Apgar score <7 in women with elevated SUA (exposed group)

$p_2$ = (3.8%) proportion of neonates with Apgar score <7 in women with normal SUA (unexposed group)

Substituting for the above figures the minimum sample size required was 165 (55 women with elevated SUA and 110 women with normal SUA).

- $\bar{p} = \frac{(p_1-p_2)}{2} = \frac{(0.183-0.038)}{2} = 0.1105$
- $n_1 = \frac{(1+2)}{2} \frac{0.1105(1-0.1105)(0.84+1.96)^2}{(0.183-0.038)^2} = 55$
- $n_2 = n_1 \times r = 110$
- $n = n_1 + n_2 = 165$

A total number of 55 PE women with high uric acid and a total of 110 PE women with normal uric acid were recruited in the study. Approximately 165 PE pregnant women with PE were enrolled in the study.

### 3.6 Sampling Method

In MTRH RMBH approximately 4 mothers with PET were seen every day in the year 2022. And for every 4 mothers with PET seen in a day there were approximately three women with normal uric acid and one woman with elevated uric acid (1:3). 1386 PET mothers were seen during the year 2022 (346 had elevated uric acid and 1038 had normal uric acid). Therefore the study used a systematic random sampling technique to sample the patient in exposed and non-exposed group where every $6^{th}$ PET mother with elevated uric acid and every $9^{th}$ PET mother with normal uric acid was recruited into the study.

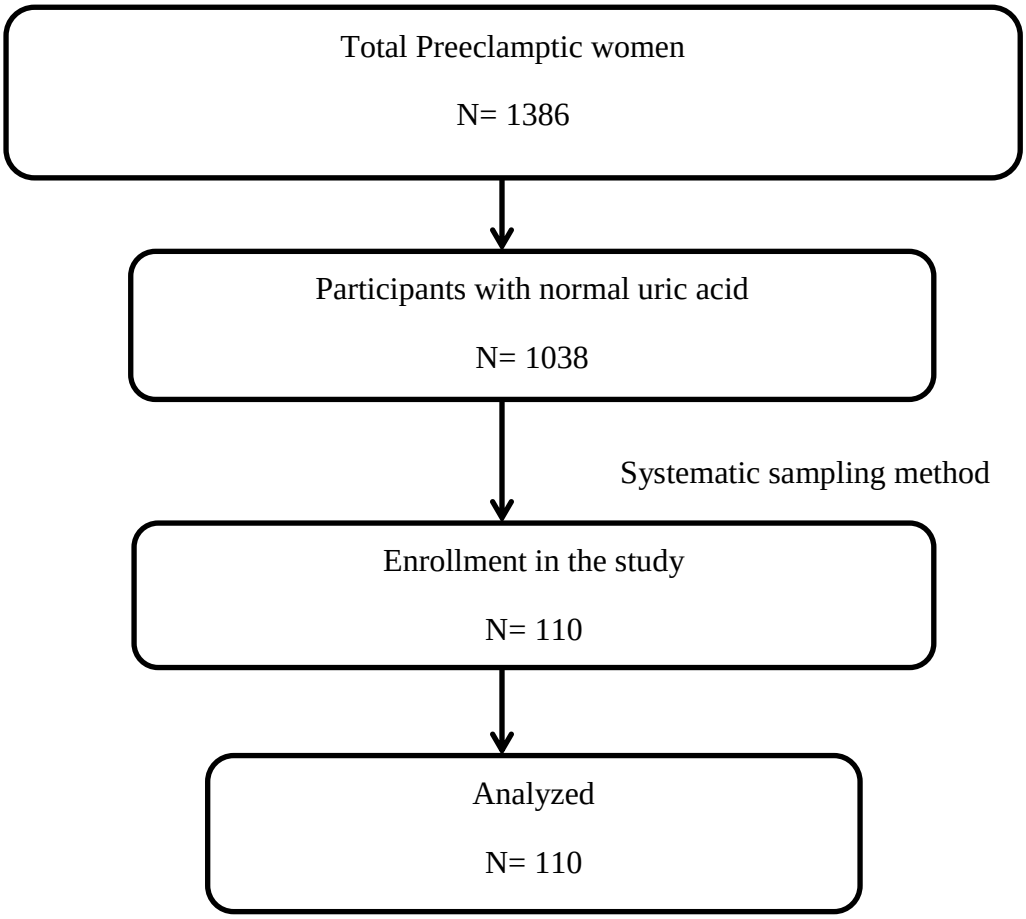
#### 3.6.1 Sampling Procedure

The study sample was subdivided into exposed and non-exposed groups. In this study women with PET with normal uric acid (UA) were the non-exposed group while women with PET and elevated uric acid formed the exposed group. Matching for the 2 groups was done based on parity and gestation age. Parity was matched to the exact parity of the exposed and non-exposed while gestation age was matched with an allowance of ± two weeks.

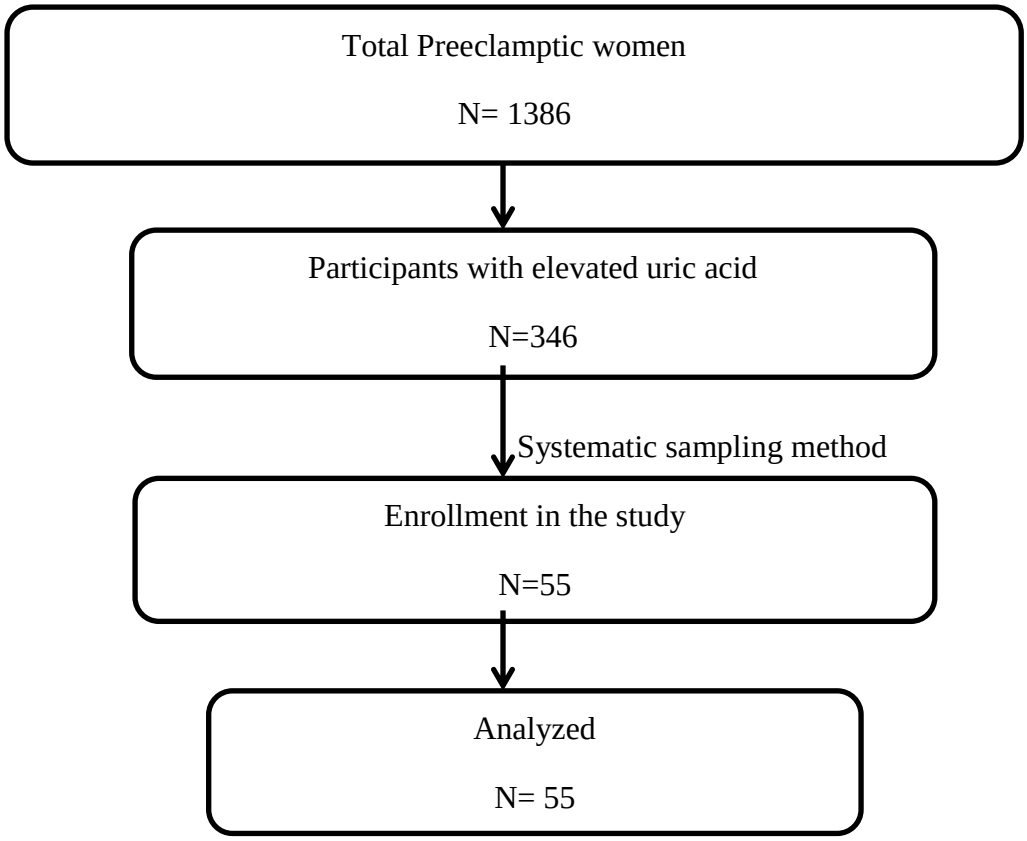
The exposed and non-exposed were selected using systematic sampling technique. Hence the sampling interval was k = N/n = 346/55=6.3, thus every sixth PET mother with elevated uric acid was selected into the exposed group. And sampling interval in non-exposed group was k = N/n = 1038/110= 9.4, thus every ninth PET mother with normal uric acid was selected into non-exposed group. The first participant in exposed group was selected randomly by having 6 folded papers numbered 1 to 6 and one selected randomly (The first one selected was 2). Then every subsequent 6th patient was then selected to form the exposed group. If the 6th subsequent participant did not

meet the eligibility criteria, the immediate next was selected and subsequently every other 6th thereafter was selected until the sample size was attained. The first participant in non-exposed group was selected randomly by having 9 folded papers numbered 1 to 9 and one selected randomly (The first one selected was 1). Every subsequent 9th patient was then selected to form the non-exposed group. If the 9th subsequent participant did not meet the eligibility criteria, the immediate next was selected and subsequently every other 9th thereafter was selected till the sample size was attained.

### 3.6.2 Enrolment Procedure non-Exported



### 3.6.2 Enrolment Procedure Exported




### 3.7 Pilot study

Pilot study means pre-testing the instruments with a few respondents to test their accuracy. This was done to determine the validity and reliability of the instruments. The pilot study was carried out at Webuye County Referral Hospital, two week prior to commencement of the study. Explicitness and analyzability of the questions was determined and terminologies deemed difficult was simplified. The questionnaire was administered to 16 mothers (10% of sample size). The Karl Pearson product moment correlation coefficient was obtained and then reliability of the research instrument assessed

### 3.7.1 Validity of the Study Instruments

Validity is the degree of accuracy to which a test measures what it purports to measure (Kirk & Miller, 2009). In this study, content validity of the instruments was considered. Content validity addresses how well the items developed to operationalize a construct provide an adequate and representative sample of all the items that might measure the construct of interest (Mbwesa, 2006). Because there is no statistical test to determine whether a measure adequately covers a content area or adequately represents a construct, the pilot study questionnaires was scrutinized to identify items that seem unclear or ambiguous to the respondents. The researcher validated the questionnaire by subjecting it to a rigorous scrutiny by senior research experts from Moi University.

### 3.7.2 Reliability of the Study Instruments

Reliability of an instrument is the degree of consistency with which it measures a variable. It is concerned with estimates of the degree to which a research instrument yields consistent results or data after repeated trials (Kothari, 2004). The test-retest technique of reliability testing was used to assess the reliability of the research instruments. The questionnaire was administered to the pilot sample respondents twice, with a one-week interval, after which the researcher compared the two sets for each respondent to find out whether the responses are consistent. This enabled the researcher to restructure the questionnaire by incorporating the missing information, omitting irrelevant questions and paraphrasing questions that will appear ambiguous to respondents. This was done under the guidance of the supervisors. A correlation coefficient for the two tests was calculated using the Pearson Correlation Coefficient formula. A reliability coefficient of at least 0.7 was accepted as recommended by Mugenda & Mugenda (2012). If the correlation coefficient is less than 0.7, then the

content of the instrument was improved.

### 3.8 Data collection Tool and procedure

The data collection was done in RMBH, MTRH postnatal ward by investigator with the assistance of the research assistant. The research assistants were trained on research protocols governing this study as well as rules governing any study being undertaken in MTRH. They were informed of the study to be conducted and purpose of the study was explained. A researcher administered structured questionnaire was used to extract quantitative data from the respondent.

After proper Institutional Ethical Clearance, the researcher introduced herself to clinical team in the reproductive unit and explained the purpose of her study. The researcher went through the records and identified postpartum women who were admitted in postnatal ward with preeclampsia. The research team (principle investigator and the research assistant) then screened and recruited PET women into the study according to the eligibility criteria. The Blood Pressure (BP) was measured and recorded using a mercury sphygmomanometer according to the recommendation of Guideline for the management of Hypertensive disorders and as a marker of preeclampsia severity; Systolic Blood Pressure (SBP) and DBP was recorded. Then after those pregnant women with a SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg recorded twice 4 hours 30 apart or a single measurement of ≥ 160/110 mmHg, accompanied by significant proteinuria was considered as severe preeclamptic(cases) and out of this pregnant women, those with the blood pressure of ≥ 160 mmHg (SBP) or 110 mmHg (DBP) and associated proteinuria of ≥ 0.3 grams(+1 on dipstick) and with severity signs in a clinical examination such as new-onset cerebral or visual disturbance, epigastric or right upper quadrant pain and pulmonary edema considered

as severe preeclamptic and those whose blood pressure less than 160 mmHg (SBP) or 110 mmHg (DBP) with proteinuria greater than ≥ 0.3, grams(+1 on dipstick), was considered as non-severe preeclampsia.

Those who met the eligibility criteria and had serum uric acid (SUA) results in the file were approached by the research team, informed about the goal of the research, benefits and risks. Those who consented were recruited in the study and grouped into exposed (PET mothers with high uric acid) or unexposed (PET mothers with normal uric) acid group based on the SUA levels.

Uric acid is reported in Umol/L in MTRH Laboratory where normal range is below 340Umol/L (5.76 mg/l). The first participant was chosen randomly and every 7$^{th}$ woman and 9$^{th}$ PET woman in exposed and non-exposed respectively who met the eligibility criteria was approached for possible recruitment. This was done for both groups separately until the sample size was achieved.

**Table 1: Reference levels for normal serum uric acid levels**

| Unit | Non-pregnant Women | First Trimester | Second Trimester | Third Trimester |
|---|---|---|---|---|
| **mg/dl** | 2.5-5.6 | 2-4.2 | 2.4-4.9 | 3.1-5.76 |
| **umol/l** | 149-333 | 119-250 | 143-292 | 184-375 |

**(Adopted according to Abbassi-Ghanavati M, (2009).**

Recruited patients were divided into two groups: PE mothers with normal uric acid (group 1) and PE mothers with high uric acid (group 2), based on the criteria by Abbassi-Ghanavati M, 2009, as shown in table 1 below. Conversion factor is 0.059.

Recoding of demographic factors, the severity of preeclampsia, placental abruption, preterm labor, HELLP syndrome, eclampsia, ICU admission, organ failure and maternal mortality and morbidity was considered as maternal complications was done using a researcher administered questionnaire. Fetal complications that were collected and recorded included

fetal growth restriction, LBW, perinatal death, admission in the neonatal intensive care unit, and Apgar score <7 at one and five minutes. This was done for both exposed and non-exposed group.

Upon completion the questionnaires were assessed for completeness and seeked clarification as well as rectify where incomplete entries exist by the principal investigator together with two trained research assistants.

### 3.9 Data management plan

#### 3.9.1 Data collection and storage

Data was collected using a researcher administered structured questionnaire and entered into an electronic Microsoft access database. The database was encrypted to ensure confidentiality of the data and the password was made available to the principal investigator alone. Back up of the data was done to cushion against data loss. The questionnaires were kept in a safe cabinet under lock and key and access allowed to the principal investigator alone and they will be shredded after five years.

#### 3.9.2 Dissemination plan

The study findings will be prepared as a manuscript and submitted for publication in peer reviewed journals and will be presented and submitted to Moi University, School of medicine, to Moi Teaching and Referral Hospital referral hospital so as to provide more insights on already existing information on use of uric acid as parameters in predicting preeclampsia complications in pregnant woman. Furthermore, the results will be presented at workshops and scientific conferences relevant to the topic, and the protocol on the management of preeclampsia will be revised and adopted for local implementation. International standards of weights and formats will be used to ensure accessibility and easy use of data.

### 3.10 Data Analysis

Data was entered into excel sheet using double data entry to maintain accuracy. It was then exported to SPSS version 21 for analysis. Descriptive statistics such as the mean and the corresponding standard deviation was used to summarize the continuous variables such as age and gestational age among others. Categorical data such as education level, occupation, marital status, parity, gestation, blood pressure were summarized as frequency and percentages. At bivariate level, Chi Square and Fisher's exact test were done to compare uric acid and other categorical variables like gestation age. Multivariable logistic regression was done to determine factors associated with uric acid. All statistical analysis were performed at 95% confidence level

### 3.11 Quality control

1. Research assistants were trained by the principal investigator. The principal investigator routinely monitored the collected data for consistency and quality of the interviewing process;
2. Meetings with research assistants were routinely held to address data collection problems.

### 3.12Ethical considerations

All ethical issues were upheld. The Ethical approval was provided by Moi Teaching and Referral Hospital Institutional Research and Ethical Committee (IREC). The approval is based on the provision of Helsinki Declaration (2000) and on the agreement that patient anonymity must be maintained, good laboratory practice/quality control ensured, and that every finding would be treated with utmost confidentiality and for the purpose of the research only.

Permission to carry out the study was sought from MTRH management and the

Department of Reproductive Health. The researcher ensured that there was voluntary participation and a written informed consent obtained. All respondents participated on their own free will and that they were fully informed regarding the procedures of the research project and any potential risks and benefits. Upon acceptance to participate in the study, the respondents were given a written informed consent form for signing. Confidentiality and anonymity of the respondents was guaranteed. The respondents were assured of confidentiality before data was gathered from them. The identities of the respondents were protected using numbers. In order to build trust the investigator and research assistants explained to the respondents the importance of the study.

# CHAPTER FOUR

## 4.0 RESULTS

Two hundred and four participants were initially approached and screened for inclusion into the study. After which 19.1% of the participants were excluded while 165 participants were finally recruited. The flow chart of the participant is shown in Figure 1. The participants were then categorized into two groups: group A which comprised 55 (33.3%) preeclamptic women with elevated uric acid (EUA) arm and B comprised 110 (66.7%) preeclamptic women with normal uric acid arm (NUA).

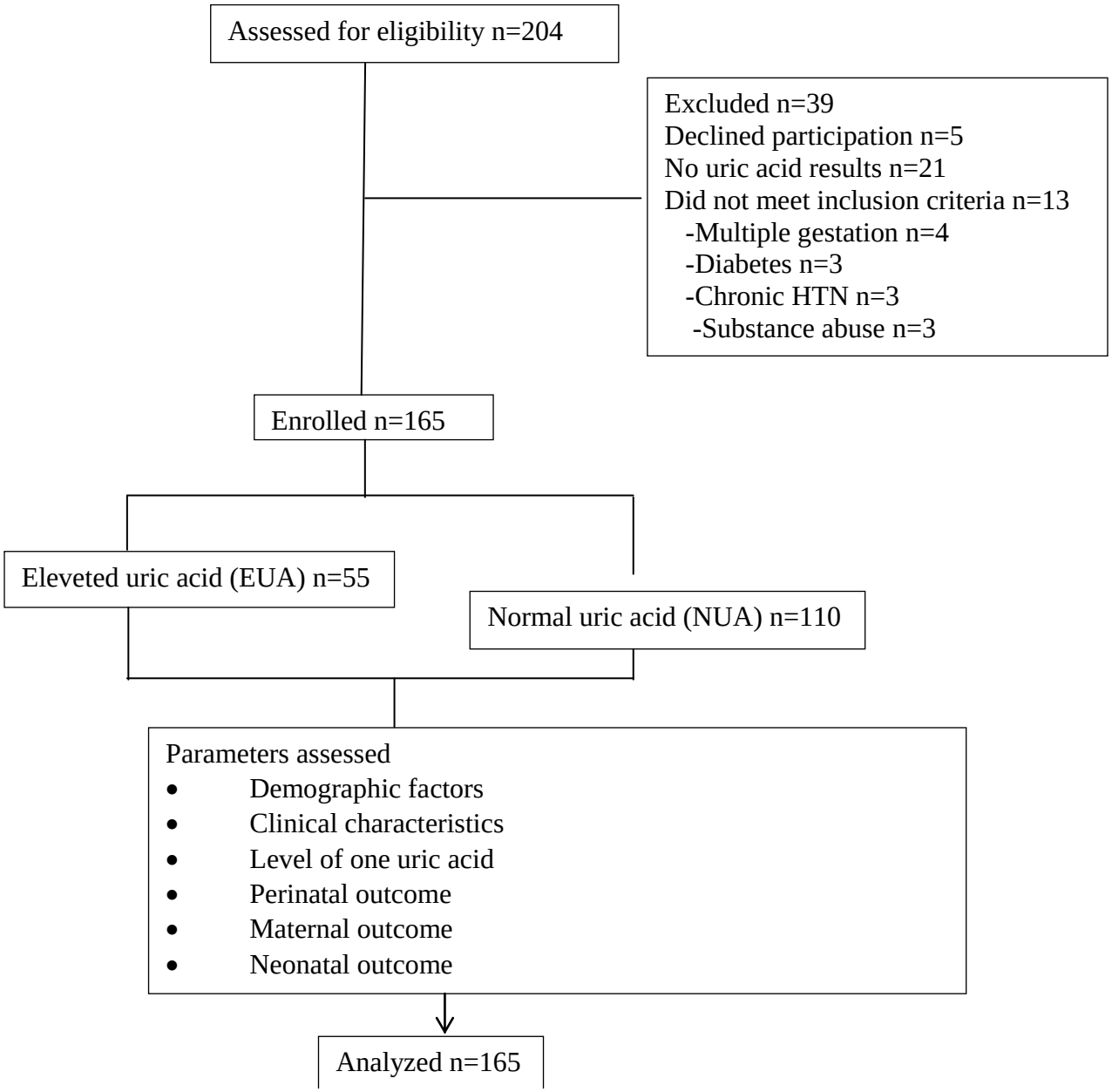



**Figure 4: The Flow pattern of serum uric acid levels and pregnant outcomes among preeclamptic women**

### 4.1 Maternal characteristics in PET women with High and normal uric acid

#### 4.1.1 Socio Demographic Characteristics

A total of 165 participants were enrolled in the study. Table 2 shows the socio demographic characteristics of the participants by the levels of uric acid. The mean age was slightly higher (29.6 ±6.3 years) among those with normal uric acid compared to those with elevated uric acid (28.8 ±6.9 years). There were no significant differences in maternal age, education level residence, occupation and marital status between EUA group and NUA group.

**Table 2: Socio demographic of the participants Overall (N=165)**

| Variable | Category | NUA group N (%) | EUA group N (%) | Total | p-value |
|---|---|---|---|---|---|
| Maternal age in Categories in years | <35 | 72 (76.6) | 37 (71.2) | 109 (74.7) | 0.469* |
| | ≥35 | 22 (23.4 | 15 (28.8) | 37 (25.3) | |
| Education level | Primary | 24 (22) | 12 (22.6) | 36 (22.2) | 0.432* |
| | Secondary | 50 (45.9) | 29 (54.7) | 79 (48.8) | |
| | Tertiary | 35 (32.1) | 12 (22.6) | 47 (29) | |
| Residence | Urban | 60 (55.6) | 29 (52.7) | 89 (54.6) | 0.732* |
| | Rural | 48 (44.4) | 26 (47.3) | 74 (54.4) | |
| Marital status | Married | 85 (79.4) | 45 (81.8) | 130 (80.2) | 0.719* |
| | Not married | 22 (20.6) | 10 (18.2) | 32 (19.8) | |
| Occupation | Business | 26 (27.4) | 11 (22.5) | 83 (57.6) | 0.056** |
| | Unemployed | 49 (51.6) | 34 (69.4) | 37 (25.7) | |
| | Employed | 14 (14.7) | 1 (2) | 15 (10.4) | |
| | Farmer | 6 (6.3) | 3 (6.1) | 9 (6.3) | |

* Chi Square test
** Fisher's exact test
[t] *t*-test
NUA normal uric acid
EUA Elevated uric acid

### 4.2 Comparison of clinical characteristics in women with EUA and NUA

Table 3 shows the clinical characteristic of PE women with EUA and NUA. Parity, personal history of PE and family history of PE were not statistically significant in the two groups. Most of the participants in NUA group (95%) and EUA group (98%) had attended ANC whereas 64.9% participants in NUA group had attended over 4 times compared to 35.1% in EUA who indicated they had attended more than 4 times. 87.3% participants from both groups indicated they had attended the ANC clinic in public hospitals and only 12.7% indicated had attended ANC in private hospitals. There was a statistically significant difference in gestation by LMP ($p < 0.001$) and gestation by ultrasound ($p < 0.001$) observed between PET women with EUA and NUA groups.

**Table 3: clinical characteristics of the participants in EUA and NUA groups**

| Variable | Category | NUA group | EUA Group | p-value |
|---|---|---|---|---|
| Parity | Para0 | 42 (63.6%) | 24 (36.4%) | 0.600* |
| | Para 1-4 | 57 (70.4%) | 24 (29.6%) | |
| | Grand multiparous | 11 (61.1%) | 7 (38.9%) | |
| Personal H/o PE | Yes | 25 (61%) | 16 (39%) | 0.373* |
| Family History of PE | Yes | 44 (69.8%) | 19 (30.2%) | 0.497* |
| ANC attendance | Yes | 105 (95%) | 54 (98%) | 0.665** |
| | No | 5 (5%) | 1 (2%) | |
| ANC place | Private clinic | 14 (66.7%) | 7 (33.3%) | >0.99* |
| | Public hospital | 96 (66.7%) | 48 (33.3%) | |
| Number of ANC visits | 4+ | 48 (64.9%) | 26 (35.1%) | 0.740* |
| | 0-3 | 62 (68.1%) | 29 (31.9%) | |
| GA by LMP | <37 weeks | 21 (47.7%) | 23 (52.3%) | 0.001* |
| | >37weeks | 76 (76.8%) | 23(23.2%) | |
| GA by US | <37 weeks | 37 (49.3%) | 38 (50.7%) | <0.001** |
| | 37-38 weeks | 5 (100%) | 2 | |
| | >38 weeks | 17 (100%) | 1 | |

### 4.3 Maternal Results at admission

As shown in table 4; majority (96 and 41 participant from NUA and EUA group respectively) of the participants from both groups did not have any documented medical conditions. Two participants from EUA group had had cardiac disease and on from NUA group had cardiac disease. Most participants from EUA group presented with high (+++) levels of proteinuria (43.2%), and33.3% had mild proteinuria (+) and the difference in these proportions was statistically significant p value of 0.035. There were no differences in SBP and DBP at admission in the two groups.

**Table 4: Results at Admission (N=165)**

| Variable | Category | NUA group | EUA group | p-value |
|---|---|---|---|---|
| **SBP** | Mean (SD) | 157.2 (13) | 157.2 (18.7) | 0.985t |
| | Range | 135 – 208 | 102 – 223 | |
| **DBP** | Mean (SD) | 98.3 (14.6) | 98.8 (14.4) | 0.860t |
| | Range | 43 – 159 | 47 – 126 | |
| **Level of Proteinuria** | + | 20 (66.7%) | 10 (33.3%) | 0.035* |
| | ++ | 38 (82.6%) | 8 (17.4%) | |
| | +++ | 21 (56.8%) | 16 (43.2%) | |
| **Documented medical condition** | No medical condition | 96 | 41 | |
| | Other | 2 | 2 | |
| | Cardiac | 1 | 2 | |

### 4.4 Intrapartum Findings

Table 5 shows clinical characteristic of participants during labor. Most of the participants in EUA group underwent caesarean section (31) compared 24 participants in NUA group, and this was statistically significant (p=0.003). The reasons for why they underwent the CS included: Fetal distress (61.5 %%), Poor maternal condition (44.1%), Poor progress (40%), Poor bishop scores (20%). There were no differences in intrapartum systolic and diastolic blood pressures in the two groups. Most of the women in EUA group (66.6%) had induced labor compared to 33.45 in NUA group, but this was not statistically significant and some of the reasons for IOL were; sever PE, term pregnancy and poor maternal condition.

**Table 5: Intrapartum (N=165)**

| Variable | Category | NUA group | EUA group | p-value |
|---|---|---|---|---|
| SBP intra | Mean (SD) | 147.6 (14.4) | 148.6 (19.5) | 0.489t |
| | Range | 49 - 177 | 93 - 206 | |
| DBP intra | Mean (SD) | 93.4 (11) | 95.1 (15.9) | 0.101t |
| | Range | 60 -114 | 60 - 161 | |
| Induction labor | Yes | 40 (66.6%) | 20 (33.4%) | 0.611* |
| | No | 70 (65%) | 35 (35%) | |
| Indication for | Severe PE | 24 | 17 | |
| Induction | Term pregnancy | 20 | 3 | |
| | Poor maternal condition | 4 | 1 | |
| Mode of delivery | CS | 24 (43.6%) | 31 (56.4%) | 0.003* |
| | SVD | 86 (78.2%) | 24 (21.8%) | |
| Indication for CS | Poor bishop scores | 3 (60%) | 2 (40%) | |
| | Poor progress | 8 (80%) | 2 (20%) | |
| | Abruption placenta | 4 (100%) | 0 | |
| | Fetal distress | 19 (55.9%) | 15 (44.1%) | |
| | Poor maternal condition | 5 (38.5%) | 8 (61.5%) | |

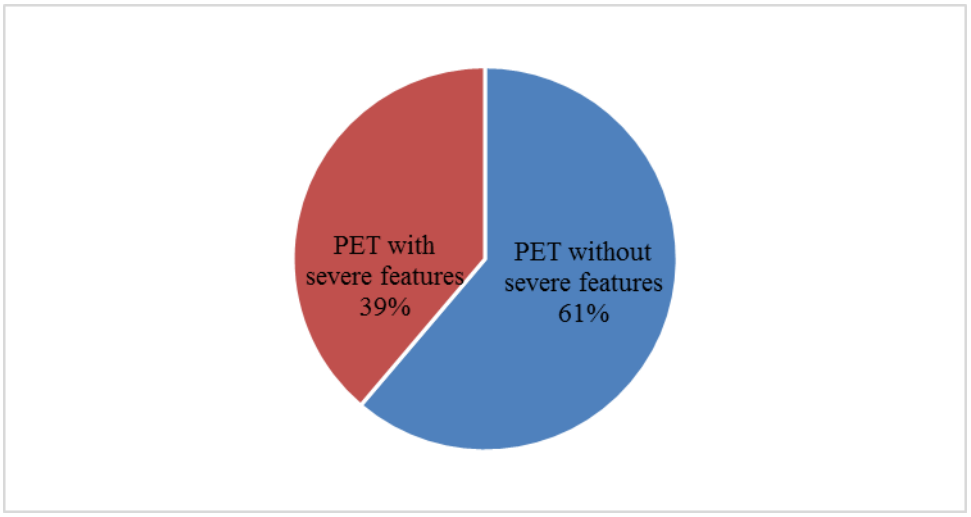



**Figure 5: Shows the respondents characteristic by severity of preeclampsia**

The figures shows that most of the respondents (61%) presented with PET without severe features and 39% of the respondents presented with PET with severe features

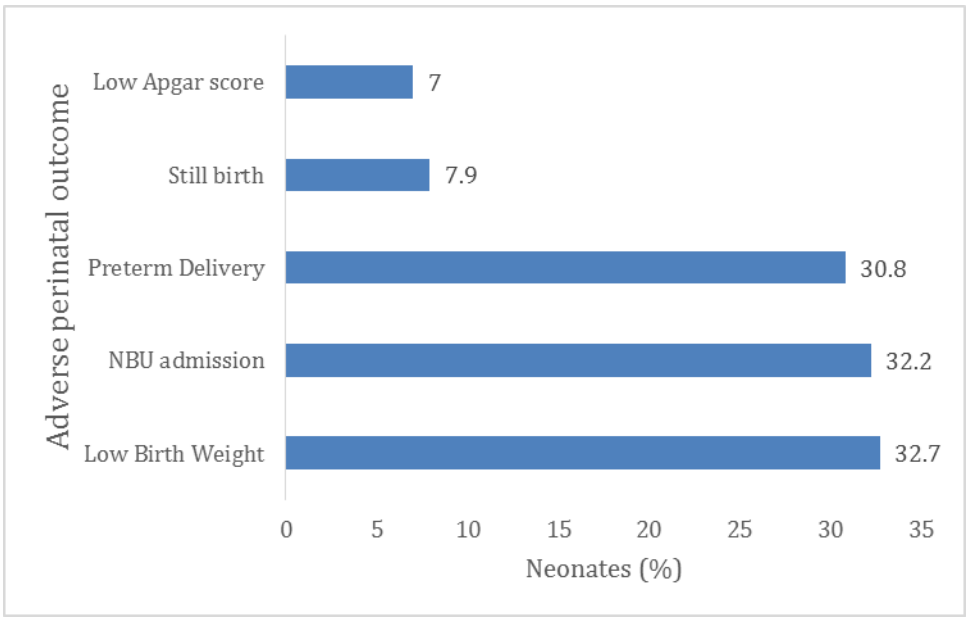



**Figure 6: Shows perinatal outcomes in preeclamptic women**

Figure 6 shows the percentage perinatal outcome in preeclamptic women. As shown in the figure most of the perinatal outcomes were low birth weight (32.7%),NBU admission (32.2%) and preterm delivery (30.8%) with the least perinatal outcomes of low APGAR scores (7%) and still birth (7.9%).

### 4.5 Objective 1: Association of levels of uric acid with severity of pre-eclampsia

The mean uric acid levels for those with elevated uric acid was 492.8 ±74.1 (median 473, IQR 437, 537.4) while the mean uric acid for those with normal uric acid was 296.3 ±41.5 (median 306.4 IQR 260.4, 334.6).

Table 6 shows a significant association between serum uric acid levels and severity of PE (p=0.013) where women with EUA levels (>340umol/l) were found to be 2.6 times more likely to have severe preeclampsia than those with the NUA levels.

**Table 6: Association between serum Uric acid levels and severity of PE**

| PE grades | Uric acid levels | | | |
|---|---|---|---|---|
| | >340umol/l | <340umol/l | OR/CI 95% | P values |
| PE with severe features | 33 (51.6%) | 31 (48.4%) | 2.6(1.7-140) | 0.013* |
| PE without severe features | 22 (21.8%) | 79 (78.2%) | 1.4(0.9-4.0) | |

### 4.6 Objective 2: Comparison of perinatal outcomes in EUA and NUA in preeclamptic women in Moi Teaching and Referral Hospital.

The perinatal outcome in NUA group and EUA group are summarized in table 7. About 70% of the neonates born from preeclamptic women with elevated UA were admitted in NBU compared to that 30% with normal UA and the difference was statistically significant even after adjusting for delivery in weeks (P< 0.001). Those neonates born with a birth weight below 2500grams were more in EUA group (73.7%) as compared with those in NUA group (26.3%) and it was statistically significant (P< 0.001). The risk of LBW in EUA group was triple that in NUA group and the difference was statistically significant (73.7% vs. 26.3%, p< 0.001). The incidence of fetal non-viability (MSB (13.5%) and FSB (3.3%)) and neonatal death 0.9% were higher in PE women with elevated UA as compared to normal UA (1.8%, 0.0%, 0.0% respectively) but they were statistically insignificant. There was a

statistical difference in APGAR scores <7 at five minutes in the two groups (p=0.052).

**Table 7: Comparison of perinatal outcomes in EUA and NUA in preeclamptic women.**

| Variable | Elevated (N=55) | Normal (N=110) | Total (N=165) | p value |
|---|---|---|---|---|
| **Fetal non-viability** | | | | |
| FSB and MSB | 11 (77.1%) | 3 (22.9%) | (8.4%) | 0.010 |
| **Neonatal death** | 4 (3.6%) | 0 (0.0%) | 4 (3.6%) | < 0.001 |
| **NICU admission** | 26 (67.8.0%) | 12 (32.2%) | 28(23%) | < 0.001 |
| **APGAR 1min** | 5.4 (0-6) | 9 (>6-10) | | < 0.001 |
| **APGAR 5min** | | | | 0.052 |
| <7 | 36 (85.7%) | 5 (4.9%) | 41 (28.3%) | |
| >7 | 6 (14.3%) | 98 (95.1%) | 104 (71.7%) | |
| **LBW** | 37 (73.7%) | 13 (26.3%) | 55 (33.3%) | < 0.001 |
| **Birth weight** | | | | |
| <2500 | 37 (73.7%) | 13 (26.3%) | 53 (30.3%) | < 0.001 |
| >=2500 | 18 (42.3%) | 94 (77.9%) | 112 (69.7%) | |

### 4.7 Objective 3: Comparison of maternal outcomes in EUA and NUA in preeclamptic women at Moi teaching and Referral hospital.

As shown in table 8 we compared the difference in maternal complications between PE women with NUA and EUA groups. The incidence of severe maternal outcome complications was significantly higher in EUA group than NUA group (62.7% vs. 37.3%) and it was statistically significant (p< 0.001). The study found that the incidences of renal failure, eclampsia, cerebral hemorrhages, abruptio placenta, HELLP syndrome and preterm labor were slightly higher in EUA group than NUA group as shown in table 8, we also found that there were no women with pregnancy complicated with cerebral hemorrhage in NUA group.

A total of two (66.7%) women in NUA group were admitted in ICU compared with one (33.6%) woman in EUA group who was admitted in ICU and it was not statistically significant (p> 0.99). There was no statistical differences in maternal death in the two groups (p=0.99).

**Table 8: Comparison of maternal outcomes in EUA and NUA in preeclamptic women.**

| Variable | Category | Elevated | Normal | p-value |
|---|---|---|---|---|
| PE severity | PET | 22 (21.8%) | 79 (78.2%) | <0.001 |
| | PET with severe features | 33 (51.6%) | 31 (48.4%) | |
| Severe maternal complication | Yes | 37 (62.7%) | 22 (37.3%) | <0.001 |
| Renal failure | Yes | 10 (41.7%) | 14 (58.3%) | |
| Eclampsia | Yes | 8 (53.3%) | 7 (46.7%) | |
| Cerebral hemorrhage | Yes | 1 (100%) | 0 | |
| Abruption placenta | Yes | 1 (33.3%) | 2 (66.7%) | |
| HELLP syndrome | Yes | 18 (51.4%) | 17 (48.6%) | |
| Preterm labour | Yes | 8 (72.7%) | 3 (27.3%) | 0.053* |
| ICU admission | Yes | 2(66.7%)) | 1 (33.3% | >0.99 |
| Maternal death | Yes | 1 (50%) | 1 (50%) | >0.99 |

## 4.8 Associated between serum uric acid and maternal and perinatal outcomes among PET mothers who presents with high uric acid levels in MTRH.

### 4.8.1 Relationship between uric acid and maternal factors

As shown in table 9, there was no association between serum uric acid and maternal factors such as age, parity, family history of PET, admission SBP, place and frequency of ANC attendance or modes of delivery. The only associated factors include previous history of PET, GBD <34 weeks, DBP <90 (OR 2.6, 95% CI, 0.99-7.2, p =0.055; OR 3.2, 95% CI, 0.09-4.52, p=0.0001; OR 2.5, 95% CI 0.016-4.02 p=0.051 respectively.

**Table 9: Relationship between uric acid and maternal factors**

| **Maternal factors** | | | AOR (95 CL) | p value |
|---|---|---|---|---|
| Maternal age | Elevated | Normal | | |
| <35 years | 43 | 89 | 0.9(0.31-2.5) | 0.84 |
| ≥35 years | 12 | 21 | 1 | |
| Parity | | | | |
| Primigravida | 24 | 42 | 0.8(0.19-4.5) | 0.89 |
| Multigravida | 31 | 68 | 1.5(0.3-6.37) | 0.52 |
| $FH_X$ of PE | | | | |
| Yes | 19 | 44 | 0.69(0.3-1.53) | 0.36 |
| Previous PET | | | | |
| Yes | 16 | 29 | 2.6(0.99-7.2) | 0.051* |
| GBD | | | | |
| 28< 34 weeks | 27 | 23 | 3.2(0.09-4.52) | 0.0001* |
| 34>37 weeks | 5 | 18 | 1.0(0.32-3.73) | 0.88 |
| >37 weeks | 23 | 69 | 1 | |
| DBP | | | | |
| >90mmHg | 44 | 25 | 2.5(0.061-4.02) | 0.055* |
| <90mmHg | 9 | 85 | 1 | |
| SBP | | | | |
| <140mmHg | 10 | 25 | 1.2(0.4-3.26) | 0.68 |
| ≥140mmHg | 45 | 85 | 1 | |
| ANC place | | | | |
| Private clinic | 7 | 14 | 1 | |
| Public hospital | 48 | 96 | 0.64(0.20-2.00) | 0.94 |
| ANC Times | | | | |
| Less than 4 | 29 | 62 | 1 | |
| More than 4 | 26 | 48 | 1.5(0.7-3.2) | 0.29 |
| Delivery mode | | | | |
| SVD | 24 | 73 | 2.3(1.0-5.17) | 0.42 |
| CS | 31 | 37 | 1 | |

Binary logistics analysis showing the relationship between uric acid and maternal factors. AOR -Adjusted Odds Ratio. * show significant factors.

### 4.8.2 Association between serum uric acid and prenatal and maternal outcome.

Table 10 shows multivariable logistic regression for predicting fetomaternal outcomes based on uric acid threshold of >340umol/l. After multivariable logistic regression for the effect of confounding variable i.e. after adjusting for maternal age, grades of PET and parity, hyperuricemia was still significantly associated with fetal non-viability (OR 0.39, 95% CI 0.26-4.24; p=0.010), Neonatal death (OR 3.1. 95% CI, 0.43-22.43; p=0.02), low birth weight (OR 3.81. 95% CI 1.62-9.31; p<0.001), low APGAR score (OR 1.72. 95% CI 0.467-6.12; p=0.052), admission to NBU (OR 0.3.95%CI 0.15-3.60; p<0.001) and any serious maternal complications (OR 4.39. 95% CL 2.54-9.74; P < 0.001).

**Table 10: Multivariable logistic regression for predicting perinatal outcome based of serum uric acid of >340umol/l.**

| Outcome | Crude OR (95% CI) | Odds Ratio (95% CI | p value |
|---|---|---|---|
| **Newborn outcome** | | | |
| Fetal no viability | 1.82(0.355-9.12) | 0.39(0.26-4.24) | 0.010 |
| neonatal death | 7.68(1.32-9.34) | 3.1(0.43-22.43) | 0.020 |
| **NBU admission** | | | |
| yes | 1.62(0.534-8.42) | 0.34(0.15-3.60) | < 0.001 |
| Preterm | 3.62 (1.70 – 7.69) | 6.27 (2.07 – 18.95) | 0.053 |
| **APGAR 5min** | | | |
| <7 | 5.51(1.82-16.23) | 1.72(0.467-6.12) | 0.052 |
| **Birth weight** | | | |
| <2500 | 6.367( 3.24-13.56) | 3.81(1.62-9.31) | < 0.001 |
| **Any complication** | | | |
| Yes | 7.23(3.52-12.5) | 4.39(2.54-9.74) | < 0.001 |

Serum uric acid was adjusted for maternal age, grades of preeclampsia and parity

# CHAPTER FIVE

This chapter reflects the main findings of the research in terms of its contributions to the key issues of maternal and perinatal outcomes among PET women with hyperuricemia. This was a cross section study of 165 postpartum women with preeclampsia aimed to assess the role of maternal uric acid in predicting pregnant outcomes and severity of PET.

Placental delivery remains the treatment for pre-eclampsia, therefore it is crucial to properly evaluate the severity of pre-eclampsia, study the factors that will influence the prognosis, and select the optimal delivery time to prevent poor maternal and perinatal outcome.

## 5.1 Maternal characteristics in PE women with High and normal uric acid

### 5.1.1 Socio demographic factors

The mean age was 29.6 and 28.8 for PET women with normal UA (NUA) and elevated uric acid (EUA) respectively indicated that in both groups relatively young women were likely to be affected by pre-eclampsia hence he two groups were homogenous in terms of age. Therefore, age is not an important factor affecting the presence or absence of UA in PET mothers. The findings are consistent with Obagah et al., (2020) who reported a mean age of 28 in the PET women with EUA and a slightly higher mean age of 31 for NUA. The mean ages reported in this group are slightly higher compared to Aslam et al. (2014); Kooffreh et al. (2014). A majority of PET women in both NUA and EUA groups had primary education level although it was not statistically significant. This findings concur with a study by Jikamo et al. (2022) and Ah et al., (2016) who observed that majority of women with PET with elevated UA had primary school education level. Low level of education implied low knowledge of pre-eclampsia indicating that these women were highly susceptible to

developing pre-eclampsia and associated fetal outcomes (Mekie et al., 2021). However no statistical significance difference was observed in education level indicating no association between education level and levels of uric acid in the NUA and EUA.

A majority of PET women with NUA and EUA resided in urban areas. The findings correspond to Mou et al. (2021) who observed high uric acid among women with PET who lived in urban areas. The findings contradict with Jikamo et al., (2022); Meena et al., (2019) who found that a majority of women with PET with high uric acid lived in rural areas. However no significance difference was observed in place of residence indicating no association between this variable and levels of uric acid in the NUA and EUA.

**5.2: Association between serum uric acid level and severity of PET.**

The mean serum uric acid levels in women with pre-eclampsia with severe features and pre-eclampsia without severe features in this study was 492.8 ±74.1 and 296.3 ±41.5 respectively. This showed that PET women who presented with severe features had a significantly higher UA levels when compared to PET women who presented without severe features (OR 2.6. 95% CI 1.7-14.0; P= 0.013). Similar findings were noted in the other studies done elsewhere by Sultana et al and Launghon et al who reported that severity of PET was associated with higher UA levels of 417.2 ± 94.4 and 427.6 ± 113.2 respectively (Sultana et al 2019 and Launghon et al 2020). This could be due to postulation that hypoxia and ischemia of the placenta and cytokines production which worsens with severity of PET induces the production and expression of xanthine oxidase and therefore increases the production of uric acid and also reactive oxygen species in PET women and hence causing maternal and perinatal complications.

In contrast, Chenet al. (2018) reported that serum uric acid levels increased with the onset of clinical signs of preeclampsia, but it might not be a predictor of preeclampsia severity and should not be considered as a predictive biomarker for severity of PET therefore should not be used in predicting the severity of PET (Chenet al 2018). This was attributed to the fact that Chenet al. (2018) compared women with PET and those without PET. In addition a systematic review study involving 6000 women showed low evidence of using uric acid to predict severity of pre-eclampsia as indicated by the following pooled sensitivity (Se), specificity (Sp) and diagnostics odds (DOR); Se 0.74 (95%CI 0.71-0.77), Sp was 0.66 (95%CI 0.63-0.68), and DOR was 9.67 (95%CI 4.57- 20.47) respectively (Pecoraro and Trenti, 2020).

### 5.3: Comparison between serum UA and perinatal outcomes among PET mothers in Moi Teaching and Referral Hospital.

#### 5.3.1 Neonatal outcome

Our study looked at association between serum uric acid and perinatal outcomes among the preeclamptic women and found a significant association between serum uric acid and perinatal complications.

Preeclampsia, especially associated with elevated UA can be related to hypoxia and ischemia of the placenta which results to placental insufficiency and this could result to fetal growth restriction (FGR) and low birth weight. In our study the risk of low birth weight (LBW) in EUA group was more than double that in NUA group and was statistically significant even after adjusting for gestation age (73.7% vs. 26.3%, $p< 0.001$). These was comparable to a study by Mahjabeen et al. (2019) and Obajah et al. (2020) who found out that elevated UA (427.7 ± 36.8 and 405.6 ±99.5) respectively in PET women was associated with development of low birth weight (LBW) and fetal growth restriction. In contrast Thangaratinam et al. (2019) who found no association

between EUA and occurrence of LBW which can be attributed to study design that was a systemic Review study.

In our study, it is worth noting that after adjusting for week of delivery, the risk of neonates being admitted in NICU(Neonatal Intensive Care Unit) in EUA group was significantly higher than in the NUA group and it was statistically significant (67.8%% vs. 32.2%, p< 0.001). This implies that neonates in EUA group had a higher morbidity than neonates in NUA group. This concurs with a study done by Saad et al. (2011), Mahjabeen et al. (2019), and Meena et al. (2019) that showed most of the neonates born from PET mothers with EUA were admitted in NICU. In contrast, Asgharnia et al. (2017) and Chawla et al. (2018) found no relationship between EUA and admission to NICU, but found out other factors like low platelets and abnormal liver function test to be associated with admission in NICU.

Fetal non-viability in the study was assessed in terms of a baby born as fresh still birth or macerated still birth. In our study, fetal non-viability syndrome was more in the EUA group than NUA group and it was statistically significant p value of <0.010. This shows that those fetuses born from preeclamptic women with high UA are more likely to be non-viable. These results concur with a study done by Haider et al. (2019) and Nair et al. (2017) that found a relationship between EUA and fetal non-viability at birth in preeclamptic women. However, Thangaratinam et al. (2016) and Le et al. (2019) found no association between EUA and fetal non-viability at birth. The small size sample size could have been responsible for the insignificant differences noted in the two groups.

Our study also looked at the association between serum UA and APGAR scores at 5 minutes. We found 85% of neonates of preeclamptic women who had elevated UA

(>340umol/l) had a 5 minute APGAR scores <7 in contrast to 4.9% of the neonates of PE women who had normal UA levels (<340umol/l) a p value of 0.052 which was statistically significant. These findings concur with a study done by Nesa et al. (2019) which found that the serum uric acid (SUA) of 7.03±1.89 mg/dl and 4.49±1.72 mg/dl resulted in 30% and 12% birth asphyxia (APGAR scores <7) cases in preeclampsia and normotensive respectively. Lin et al. (2019) also reported Serum uric acid levels of was >340.0 ± 119.6 μmol/L in women with hypertensive disorders was highly associated with birth asphyxia compared to Serum uric acid of 295.8 ± 81.7 μmol/L in normal women (OR 5.514, 95% CI 1.877–16.198). In contrast in a prospective case control study, high uric acid 405.6±995 μmol/L in preeclamptic women was not statistically associated with the occurrence of birth asphyxia (p=0.56) (Obagah et al., 2020). Nisar and Yoshida, (2022) in a descriptive cross-sectional study also found no significant differences (P > 0.05) between the mothers in the asphyxia group and non-asphyxia group on the following conditions; pre-eclampsia with high UA, HIV positive sero status, and Cephalo Pelvic Disproportion (CPD), suggesting that these were not associative factors for birth asphyxia (Nisar and Yoshida, 2022). This could be attributed to the fact that the study had low sample size and looked at many factors causing low APGAR scores.

## 5.4 Comparison between serum UA and maternal outcomes among PET mothers in Moi Teaching and Referral Hospital.

### 5.4.1 Maternal outcomes

Our study looked at the comparison between serum uric acid and maternal complications among the preeclamptic women. The study showed that there was a relationship between serum uric acid and maternal complications ($p<0.001$). There were 14 women with AKI, 10 with eclampsia, 2 with cerebral hemorrhage, 2 with abruptio placenta and 20 with HELLP syndrome in PET women with EUA (>340umol/l), whereas in PET with NUA (340umol/l) there were 10 women with AKI, 7 with eclampsia, no woman with cerebral hemorrhage, one woman with abruptio placenta and 15 with HELLP syndrome. This is consistent with the study done by Meena R et al. (2019) which showed that hyperuricemia in patients with hypertensive disorders during pregnancy was a strong risk factor for severe maternal complications. In the study done by Kumar and Singh, (2019) it was observed that a high uric acid level was associated with increased severity of the disease and adverse maternal outcomes (Kumar and Singh 2019). Similarly, Kondareddy and Prathap, (2016) also found that an increase in uric acid level is associated with increasing severity of pregnancy-induced hypertension like eclampsia, abruptio and HELLP syndrome. The most common maternal complication reported were HELLP syndrome, which concur with a study done by Asgharnia et al. (2017) who found that 1 mg/dl increase in blood uric acid level induced 1.74 fold increase in the risk of hepatic dysfunction an hence HELLP syndrome (OR: 1.74, 95% CI: 1.12-2.72). Ngwenya, (2017); Rewatkar et al. (2019) have also reported a common cause of maternal deaths as HELLP syndrome in pre-eclamptic women with high uric acid. These findings are contrary to Williams and Galerneau, (2002) who found that women with SUA levels 340 ± 80 umol/L did not have HELLP syndrome.

In our study preterm labor occurred more PET women with EUA than PET women with NUA and there was statistical association between serum UA and preterm labor (24.2% vs. 10.3%, p=0.053). These concur with Le et al and Asgharnia et al. (2019) who found significantly high level of uric acid in pre-eclampsia mothers led to preterm delivery (OR: 1.54, 95% CI: 1.15-2) and concluded that serum uric acid can be used as a measurement marker to assess pregnant complications like preterm labor. Our study found low maternal death in PE women with EUA and NUA group (1.8% vs. 0.9%) and it was not statistically significant p=0.99. Our findings concur with Saldanha et al. (2018) and Andrews et al. (2016) who found a low maternal mortality of 2.2% and 2.8% respectively in pre-eclamptic mothers with high SUA. Similarly Essiben et al., 2016 did a cross-sectional study in two tertiary hospitals in Cameroon showed that the maternal mortality of 05(5.1%) in pregnancy induced hypertensive (PIH) cases and out this 01(20%) maternal mortality had uric acid level > 5.5mg/dl (Essiben et al., 2016). The study concluded that serum uric acid level could not be used as a biochemical indicator of preeclampsia/eclampsia and its complications like maternal mortality (Essiben et al., 2016). However, our findings were contrary to a study done by Kumar et al. (2019) that showed high maternal mortality 62.5% in pregnant women with pre-eclamptic conditions who had serum uric acid of 6.8 ± 2.72 mg/dl compared to 0% death in the control group (Kumar and Singh, 2019). The differences in the findings could be because our study was done in referral hospital that is well equipped with specialist and facilities necessary for managing PET mother who presented with complication such as EUA in pregnancy.

**5.5 Association between serum uric acid and maternal and perinatal outcome in Preeclampsia women with high uric acid.**

In a multivariable logistic regression analysis after adjusting for maternal age, grades of PE and parity serum uric acid still remained significantly associated with severe maternal complications at threshold of > 340umol/l (4.39(2.54-9.74) p < 0.001). After adjusting for maternal age, grades of PE and parity, hyperuricemia was still significantly associated with fetal non viablity (OR 0.39, 95% CI 0.26-4.24; p=0.010), Neonatal death (OR 3.1. 95% CI, 0.43-22.43; p=0.02), low birth weight (OR 3.81. 95% CI 1.62-9.31; p<0.001), low APGAR score (OR 1.72. 95% CI 0.467-6.12; p=0.052), admission to NBU (OR 0.3.95%CI 0.15-3.60; p<0.001) and any serious maternal complications (OR 4.39. 95% CL 2.54-9.74; P < 0.001). This concurs with a cross section study done by Shiktiba in Nigeria who concluded that hyperuricemia was still significantly associated with intrauterine growth restriction (P 0.029), low birth weight (P <0.001), fetal distress (P 0.002), Intrauterine fetal death (P 0.003) and neonatal death (P 0.005). Another study done by Tam et al, (2018) found similar results that uric acid at a threshold of 393 μmol/L was a good prognostic marker for IUGR (OR 5.510, 95% CI 2.611–11.628); preterm birth (OR 3.910, 95% CI 1.696–9.011); neonatal death (OR 3.249, 95% CI 0.475–22.231); low Apgar score (OR 1.716, 95% CI 0.474–6.220); and for general fetal/neonatal complications (OR 4.399, 95% CI 2.137–9.052) (Tam et al 2018).

## 5.4 Study strength and limitations

### 5.4.1 Study strength

1. There was no differences in subjects in both arms in terms of mean age, level of education, marital status, parity and these added credit to our study

2. MTRH being a large tertiary hospital in the region with high number of patients, and application of treatment protocol of our hospital by same physician group made my study more reliable and feasible.

3. The diagnosis of PET was done by qualified doctor in reproductive health, serum uric acid was done in hospital lab by machines that are well standardized and with qualified staffs.

### 5.4.2 Study limitation

1. Serum uric acid was considered as a single variable without considering relevant covariant like age and body mass index.

2. The data was collected in a hospital centre (a tertiary obstetric care center) may be over- represented by more severe PE patients and therefore cannot be generalized in the whole population.

# CHAPTER SIX

## 6.0 CONCLUSIONS AND RECOMMENDATIONS

### 6.1 Conclusions

Cognizant to the findings in this study discussed in chapter 4, we conclude the following:

1. We found a significant association between serum uric acid levels and severity of PET; that is higher serum uric acid is highly associated with severe preeclampsia.
2. There was a significant association between serum uric acid levels and poor perinatal outcomes as the study found significant number of low birth weight (LBW), increased number of newborn who were admitted in NBU and fetal non-viability in PET women with elevated uric acid in comparison to PET women with normal uric acid.
3. There was a significant association between serum uric acid levels and poor maternal outcomes as the study found significant number maternal complication like kidney injuries, HELLP syndrome, placenta abruptio, cerebral hemorrhage, eclampsia, preterm labor and maternal death in PE women with elevated uric acid in comparison to PE women with normal uric acid.

## 6.2 Recommendation

1. We recommend that serum uric acid should be in evaluating severity of preeclampsia in pregnant women with PET which will inform the need for early, timely and proper management plan for the condition to prevent complications that comes with severity of the disease.
2. We recommend routine estimation of serum uric acid (which is inexpensive and easily done) in pregnant complicated with preeclampsia to predict perinatal complications and hence need for fetal surveillance to prevent poor perinatal outcome.
3. We recommend further studies, prospective large cohort studies to evaluate relationship between serum uric acid and perinatal outcome to come up with a more precise and liable results that can be generalized to the whole population in Kenya.
4. We recommend serum uric acid to be used to predict maternal and perinatal outcomes to be part of our a protocol in management of PE in our obstetric unit at MTRH.

## REFERENCES

Ah, A.K., Huri, A., Shuaib, A.A., Harazi, A.H. Al, 2016. Serum uric acid in women with preeclampsia compared to normotensive women. Sudan Med. J. 52, 114–119.

Ahmad, M., Ahmad, M.Q., Sohail, C.S., Abdullah, M., Sohail, T., Jamal, A., 2018. Social and Demographic Determinants of Mode of Delivery among Pregnant Women Visiting Gynecology Department of Jinnah Hospital Lahore, Pakistan. J. Fam. Med. Community Heal. 5, 1–8.

American College of Obstetrics and Gynecologogy guidelines on preeclampsia and eclampsia of 2018'

Ahmed, Q.N., Dewan, F., 2017. Effect of raised serum uric acid level on perinatal and maternal outcome in cases of pregnancy-induced hypertension. J. Bangabandhu Sheikh Mujib Med. Univ. 10, 58–60.

American College of Obstetricians and Gynecologists', Task Force on Hypertension in Pregnancy, 2013. Hypertension in Pregnancy.

Andarge, R.B., Anshebo, A.A., Halil, H.M., Kebede, B.A., Ahmed, R., 2020. Prevalence and Associated Factors of Pre-eclampsia among Pregnant Women at Antenatal Booking in the Halaba Kullito General Hospital , Southern Ethiopia . Journal of Women ' s Health Care. J. Women's Heal. Care 9, 1–9. doi:10.35248/2167-0420.20.9.496.

Andrews, L., Namboothiri, H., Vaishnav, S., 2016. Perinatal outcome in relation with laboratory findings in pregnancy induced hypertension ( PIH ). Int. J. Clin. Biochem. Res. 3, 105–109. doi:10.5958/2394-6377.2016.00020.4

Anna, W., Zembala-szczerba, M., Babczyk, D., Kołodziejczyk-pietruszka, M., Lewaczy, O., Huras, H., 2019. Early- and Late-Onset Preeclampsia : A Comprehensive Cohort Study of Laboratory and Clinical Findings according to the New. Int. J. Hypertens. 2019, 9.

Asgharnia, M., Mirblouk, F., Kazemi, S., Pourmarzi, D., Keivani, M.M., Fatemeh, S., Heirati, D., 2017. Maternal serum uric acid level and maternal and neonatal complications in preeclamptic women: A cross-sectional study. Int. J. Reprod. Biomed. 15, 583–588.

Aslam, H.M., Saleem, S., Afzal, R., Iqbal, U., Saleem, S.M., Waqas, M., Shaikh, A., Shahid, N., 2014. Risk factors of birth asphyxia. Ital. J. Pediatr. 1–9. doi:10.1186/s13052-014-0094-2

Aswita, A., Arsulfa, A., Melania, M., Nurmiaty, N., 2018. Uric Acid Level as Predictor Preeclampsia in Pregnant Woman at Working Area of Public Health Centers in Kendari City , Southeast Sulawesi Province. Int. J. Sci. Basic Appl. Res. 38, 237–246.

Bainbridge, S.A., Roberts MD, J.M., 2012. Uric Acid as a Pathogenic Factor in Preeclampsia. Placenta 29, 1–9. doi:10.1016/j.placenta.2007.11.001.Uric

Baranala, S.K., Kumar, N., 2020. Utility of urinary uric acid and creatinine ratio as a marker of neonatal asphyxia : a comparative assessment. Int. J. Heal. Clin. Res. 3, 149–153.

Bellos, I., Pergialiotis, V., Loutradis, D., 2020. The prognostic role of serum uric acid levels in preeclampsia : A meta-analysis. J. Clin. Hypertens. 22, 826–834. doi:10.1111/jch.13865

Bellomo, G., Venanzi, S., Saronio, P., Verdura, C., Narducci, P.L., 2011. Prognostic significance of serum uric acid in women with gestational hypertension. Hypertension 58, 704–708. https://doi.org/10.1161/hypertension.111.177212

Bhandari, S., Shetty, A., Bhattacharya, S., 2013. Maternal and perinatal consequences of antepartum haemorrhage of unknown origin. Epidemiology 2014, 44–52. doi:10.1111/1471-0528.12464

Bhongir, V.A., Yakama, V.V.A., Saha, S., Radia, S.B., Pabbati, J., 2015. The Urinary Acid/Creatinine Ratio is an Adjuvant Marker for perinatal Asphyxia. Eur J Pharm Med Res 2, 520–528.

Black, R.E., Laxminarayan, R., Temmerman, M., Walker, N., 2016. Reproductive, Maternal, Newborn and Child Health. Disease Control Priorities, third Edit. ed. Washington DC: World Bank. doi:doi:10.1596/978-1-4648-0348-2

Briana, D.D., Malamitsi-puchner, A., 2009. Intrauterine growth restriction and adult disease : the role of adipocytokines. Eur. J. Endocrinol. 160, 337–347. doi:10.1530/EJE-08-0621

Brown, S.-Z., Newby, H., Nobuko, C., Lale, M., Emi Suzuki, S., Wilmoth, J., 2013. Understanding Global Trends in Maternal Mortality. Int. Perspect. Sex. Resproductive Heal. 39, 41. doi:10.1363/3903213

Cabrera, I.B., Quiñones, J.N., Durie, D., Rust, J., Smulian, J.C., Scorza, W.E., 2016. Use of intracervical balloons and chorioamnionitis in term premature rupture of membranes. J. Matern. Neonatal Med. 29, 967–971. doi:10.3109/14767058.2015.1027191

Callister, L.C., Edwards, J.E., 2017. Sustainable Development Goals and the Ongoing Process of Reducing Maternal Mortality. JOGNN - J. Obstet. Gynecol. Neonatal Nurs. 46, e56–e64. doi:10.1016/j.jogn.2016.10.009

Chawla, R., Malik, S., 2018. Microalbuminuria Detected at Mid Term as a Marker for Adverse Pregnancy Outcome. Int. J. Heal. Sci. Res. 8, 41–52.

Connealy, B.D., Carreno, C.A., Blackwell, S.C., Sibai, B.M., Kase, B.A., Hart, L.A., 2014. A History of Prior Preeclampsia As a Risk Factor for Preterm Birth. Am. J. Perinatol. 1, 483–488.

Das, S., Das, R., Bajracharya, R., Baral, G., Jabegu, B., 2019. Incidence and Risk Factors of Pre-Eclampsia in the Paropakar Maternity and Women ' s Hospital , Nepal : A Retrospective Study. Int. J. Environ. Res. Public Health 16, 1–8. doi:10.3390/ijerph16193571

Davies, E.L., Bell, J.S., Bhattacharya, S., Davies, E.L., Bell, J.S., Bhattacharya, S., 2016. Hypertension in Pregnancy Preeclampsia and preterm delivery : A population- based case – control study. Hypertens. Pregnancy 35, 510–519. doi:10.1080/10641955.2016.1190846

Delibasi, T., Ustun, I., Aydin, Y., Berker, D., Erol, H.K., Gul, K., Unal, M., Guler, S., 2006. Early severe pre-eclamptic findings in a patient with Cushing ' s syndrome. Gynecol. Endocrinol. 22, 710–712. doi:10.1080/09513590601069447

Dekker GA, Sibai BM. Etiology and pathogenesis of preeclampsia: current concepts. Am J Obstet Gynecol 1998; 179:1359–75. (Level III)

Deshpande, H.G., Madkar, C.S., Shinde, M., Kothari, V.S., 2018. Assessment of the level of serum uric acid in patients of pre-eclampsia and their comparison with levels in normotensive pregnancy. Int. J. Reprod. Contraception, Obstet. Gynecol. 7, 4900. doi:10.18203/2320-1770.ijrcog20184937

Essiben, F., Itembe, O., Foumane, P., Nguefack, M.T. De, Eko, F.E., 2016. Blood Uric Acid Level as a Marker of Increased Risk of Eclampsia in Severe Pre-Eclamptic Patients : A Cross-Sectional Study in Two Tertiary Hospitals of Yaoundé , Cameroon. J. Heal. Sci. 7–11

Falavina, L.P., Oliveira, R.R. De, Melo, E.C., Mathias, A.D.F., 2018. Hospitalization during pregnancy according to childbirth financial coverage : a population-based study. J. Sch. Nusring Univ. SAO PAULO 52, 1–8.

Falcão, I.R., Ribeiro-Silva, R.D.C., De Almeida, M.F., Fiaccone, R.L., Dos S. Rocha, A., Ortelan, N., Silva, N.J., Paixao, E.S., Ichihara, M.Y., Rodrigues, L.C., Barreto, M.L., 2020. Factors associated with low birth weight at term: A population-based linkage study of the 100 million Brazilian cohort. BMC Pregnancy Childbirth 20, 1–11. doi:10.1186/s12884-020-03226-x

Fukami, T., Koga, H., Goto, M., Ando, M., Matsuoka, S., Tohyama, A., Yamamoto, H., Nakamura, S., Koyanagi, T., To, Y., Kondo, H., Eguchi, F., Tsujioka, H., 2019. Incidence and risk factors for postpartum hemorrhage among transvaginal deliveries at a tertiary perinatal medical facility in Japan. PLoS One 14, 1–8. doi:10.1371/journal.pone.0208873

Gabkika, B., Souam, N., Adrienne, N., Yannick, A., 2018. Birth asphyxia in fullterm neonates in n ' djamena mother and child hospital ( Chad ). Med. Res. 4, 151–153.

Gomathy, E., Akurati, L., Radhika, K., 2018. Early onset and late onset preeclampsia-maternal and perinatal outcomes in a rural teritiary health center. Int. J. Reprod. Contraception, Obstet. Gynecol. 7, 2266–2269.

Gowri, V., Al-Zakwani, I., 2010. Prevalence of cesarean delivery in preeclamptic patients with elevated uric acid. Hypertens. Pregnancy 29, 231–235.

Guerrier, G., Oluyide, B., Keramarou, M., Grais, R.F., 2013. Factors associated with severe preeclampsia and eclampsia in Jahun , Nigeria. Int. J. Womens. Health 509–513. doi:10.2147/IJWH.S47056

Haider, R., Col, L., Rahman, A., Islam, F., Akhter, M., Wahed, F., 2019. Clinical Study of Serum Uric Acid Level on Outcome of Pregnancy in Cases of Pregnancy Induced Hypertension ( PIH ). Int. J. Med. Res. Prof. 5, 40–43. doi:10.21276/ijmrp.2019.5.5.029

Hodgins, S., 2015. Pre-eclampsia as Underlying Cause for Perinatal Deaths : Time for Action. Glob. Heal. Sci. Pract. 3, 525–527.

Houwen, C. Van Der, Schukken, T., Pampus, M. Van, 2009. Case report Transient early preeclampsia in twin pregnancy with a triploid fetus : a case report. J. Med. Case Rep. 3, 2–5. doi:10.1186/1752-1947-3-7311

Huppertz, B., 2008. Placental origins of preeclampsia: Challenging the current hypothesis. Hypertension 51, 970–975. https://doi.org/10.1161/HYPERTENSIONAHA.107.107607

Jampana, K.C., Paka, A.C., Rajesh, K., 2022. Evaluation of Uric acid levels in pregnancy induced hypertension (PIH) in relation to maternal and perimatal outcomes: a teaching hospital based study. JAMP 5, 865–868. https://doi.org/10.47009/jamp.2023.5.2.183

Jamil, U., Mukhtar, A., Hussain, S., Munawar, F., 2018. PREGNANCY INDUCED HYPERTENSION; Serum uric acid as an indicator of fetomaternal complications of pregnancy induced hypertension in late pregnancy. Prof. Med. J. 25, 1168–1172. doi:10.29309/TPMJ/18.4575

Jin, M., Fan, Y., Yang, I., Yin, Y., Luo, J.J., Wang, H., Yang, X.-F., 2012. Uric Acid, Hyperuricemia and Vascular Diseases. Front Biosci 17, 656–669.

Jikamo, B., Adefris, M., Azale, T., Gelaye, K.A., 2022. Incidence of adverse perinatal outcomes and risk factors among women with pre-eclampsia, southern Ethiopia: a prospective open cohort study. BMJ Paediatr. Open 6, 1–11. https://doi.org/10.1136/bmjpo-2022-001567

Kamath, K.R., Nayak, S.R., Shantharam, M., 2014. Serum Uric acid level in preeclampsia and its correlation to maternal and fetal outcome * Correspondence Info : Int. J. Biomed. Res. 05, 5–7. doi:10.7439/ijbr

Kenny, L.C., Mccarthy, F.P., 2015. Risk factors and effective management of preeclampsia. Dove Press J. 8, 7–12.

Klinger, G., 2020. Antepartum Hemorrhage and Outcome of Very Low Birth Weight , Very Preterm Infants : A Population-Based Study. Am. J. Exp. Agric. 1–8. doi:10.1055/s-0040-1710353

Kooffreh, M., Ekott, M., Ekpoudom, D., 2014. The prevalence of pre-eclampsia among pregnant women in the University of Calabar Teaching Hospital, Calabar. Saudi J. Heal. Sci. 3, 133. https://doi.org/10.4103/2278-0521.142317

Kuba, K., Bernstein, P., 2018. ACOG Practice Bulletin No. 188: Prelabor Rupture of Membranes. Obstet. Gynecol. 131, 1163–1164. doi:10.1002/14651858.CD004735.pub4.In

Kumar, M., Jain, N., Thora, S., Kiran, T., 2017. Urinary Uric Acid / Creatinine Ratio as an Additional Early Marker for Perinatal Asphyxia. Med. Sci. Clin. Res. 05, 25137–25140. doi:https://dx.doi.org/10.18535/jmscr/v5i7.136

Kumar, N., 2016. Postpartum Hemorrhage; a Major Killer of Woman: Review of Current Scenario. Obstet. Gynecol. Int. J. 4, 1–7. doi:10.15406/ogij.2016.04.00116

Kumar, N., Singh, A.K., 2019. Maternal serum uric acid and calcium as predictors of hypertensive disorder of pregnancy: A case control study. Taiwan. J. Obstet. Gynecol. 58, 244–250. doi:10.1016/j.tjog.2019.01.014

Kusumaningrum, R.Y., Murti, B., Prasetya, H., 2019. Low Birth , Prematurity , and Pre-Eclampsia as Risk Factors of Neonatal Asphyxia. Matern. Child Heal. 4, 49–54. doi:https://doi.org/10.26911/thejmch.2019.04.01.07

Kondareddy T, T. P. Uric acid as an important biomarker in hypertensive disorders in pregnancy. Int J Reprod Contracept Obstet Gynecol. 2016;4382– 4. http://dx.doi.org/10.18203/2320- 1770.ijrcog20164348

Kyei-Nimakoh, M., Carolan-Olah, M., McCann, T. V., 2016. Millennium development Goal 5: Progress and challenges in reducing maternal deaths in Ghana. BMC Pregnancy Childbirth 16, 1–10. doi:10.1186/s12884-016-0840-0

Lakhan, H., Raheem, F., Noor, B., Abro, K.J., 2020. Fetal Outcome in Women of Pre-Eclampsia with High Serum Uric Acid Levels _ Journal of The Society of Obstetricians and Gynaecologists of Pakistan. J. Soc. Obs. Gynaecol. 10, 9–12.

Lemma, K., Misker, D., Kassa, M., Abdulkadir, H., Otayto, K., 2022. Determinants of birth asphyxia among newborn live births in public hospitals of Gamo and Gofa zones, Southern Ethiopia. BMC Pediatr. 22, 1–13. https://doi.org/10.1186/s12887-022-03342-x

Le, T.M., Nguyen, L.H., Phan, N.L., Le, D.D., Nguyen, H.V.Q., Truong, V.Q., Cao, T.N., 2019. Maternal serum uric acid concentration and pregnancy outcomes in women with pre- - eclampsia / eclampsia. Gynecol. Obstet. 144, 21–26. doi:10.1002/ijgo.12697

Li, S., Zhang, M., Tian, H., Liu, Z., Yin, X., Xi, B., 2014. Preterm birth and risk of type 1 and type 2 diabetes : systematic review and meta-analysis. Obes. Rev. 15, 801–811. doi:10.1111/obr.12214

Li, Z.N., Wang, S.R., Wang, P., 2023. Associations between low birth weight and perinatal asphyxia: A hospital-based study. Medicine (Baltimore). 102, e33137. https://doi.org/10.1097/MD.0000000000033137

Li, X.L., Guo, P.L., Xue, Y., Gou, W.L., Tong, M., Chen, Q., 2015. An analysis of the differences between early and late preeclampsia with severe hypertension Pregnancy Hypertension : An International Journal of Women ' s Cardiovascular Health An analysis of the differences between early and late preeclampsia with severe. Int. J. Women's Cardiovasc. Heal. doi:10.1016/j.preghy.2015.12.003

Lin, J., Hong, X.Y., Tu, R.Z., 2018. The value of serum uric acid in predicting adverse pregnancy outcomes of women with hypertensive disorders of pregnancy. Ginekol. Pol. 89, 375–380. doi:10.5603/GP.a2018.0064

Logan, G.G., Njoroge, P.K., Nyabola, L.O., Mweu, M.M., 2020. Determinants of preeclampsia and eclampsia among women delivering in county hospitals in Nairobi , Kenya. F1OOOResearch 9, 1–15.

Lumbiganon, P., Laopaiboon, M., Intarut, N., Vogel, J., Souza, J., Gulmezoglu, A., Mori, R., 2014. Indirect causes of severe adverse maternal outcomes : a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health. BJOG 121, 32–39. doi:10.1111/1471-0528.12647

Ma, L.H., Alexander, M., You, D., Alkema, L., Group, U.N.I., Estimation, M., 2019. Articles National , regional , and global levels and trends in neonatal mortality between 1990 and 2017 , with scenario-based projections to 2030 : a systematic analysis. Lancet Glob. Heal. 7, e710–e720. doi:10.1016/S2214-109X(19)30163-9

Madaan, S., Jaiswal, A., Acharya, N., Tayade, S., Dhok, A., Kumar, S., 2022. Role of Salivary Uric Acid Versus Serum Uric Acid in Predicting Maternal Complications of Pre- Eclampsia in a Rural Hospital in Central India : A. Cureus 14, 1–16. https://doi.org/10.7759/cureus.23360

Machano, M.M., Joho, A.A., 2020. Prevalence and risk factors associated with severe pre-eclampsia among postpartum women in Zanzibar : a cross-sectional study. BMC Public Health 20, 1–10. doi:10.1186/s12889-020-09384-z

Mahjabeen, N., Sza, N., Begum, F., Mustary, F., 2019. Effects of Hyperuricemia on Fetal Outcome in Preeclamptic Patients. BIRDEM Med. J. 9, 117–120.

Maiuolo, J., Oppedisano, F., Gratteri, S., Muscoli, C., Mollace, V., 2015. Regulation of uric acid metabolism and excretion. Cardiology.

Mbombo, E., Midigo, R., Otieno, P., Ogwayo, I., 2018. Determinants of Modes of Delivery: A Hospital based Retrospective Study in Kenya. J. Women's Heal. Care 07, 4–9. doi:10.4172/2167-0420.1000415

Meena, R., Pachori, P., Chaudhary, S., 2019. Level of serum uric acid in patients with preeclampsia compared to controls and its relation to feto-maternal outcome. Int. J. Reprod. Contraception, Obstet. Gynecol. 8, 2471–2474.

Meshesha, A.D., Azage, M., Worku, E., Bogale, G.G., 2020. Determinants of Birth Asphyxia Among Newborns in Referral Hospitals of Amhara National Regional State, Ethiopia . Pediatr. Heal. Med. Ther. Volume 11, 1–12. https://doi.org/10.2147/phmt.s229227

Mheen, L. Van De, Schuit, E., Lim, A.C., Porath, M.M., Papatsonis, D., Erwich, J.J., Eyck, J. Van, Oirschot, C.M. Van, Hummel, P., Duvekot, J.J., Hasaart, T.H.M., Groot, C.J.M. De, Bruinse, H.W., 2014. Prediction of Preterm Birth in Multiple Pregnancies : Development of a Multivariable Model Including Cervical Length Measurement. J. Obstet. Gynaecol. Canada 36, 309–319. doi:10.1016/S1701-2163(15)30606-X

Mumtaz, M., Habib, A., Tariq, G., Fatima, M., Goswami, P., Hira, A.K., 2022. Fetal Outcome among Hypertensive Disorders in Pregnant Women with Hyperuricemia. Pakistan J. Med. Heal. Sci. 16, 663–665. https://doi.org/10.53350/pjmhs22164663

Nadeem, A., Rehman, A., Sultana, N., Mehmood, R., Merum, A., Riaz, N., 2022. Fetal out comes in Pre-Eclampsia with raised Maternal Serum Uric Acid. PJMHS 16, 119–120.

N, M., K, P., GD, S., M, R., M, M., 2019. Can hsCRP be the sole investigation for predicting the severity and outcome in women with pre‐eclampsia presenting late in pregnancy? Trop. J. Obstet. Gynaecol. 36, 54–60. doi:10.4103/TJOG.TJOG

Nair, A., Savitha, C., 2017. Estimation of Serum Uric Acid as an Indicator of Severity of Preeclampsia and Perinatal Outcome. J. Obstet. Gynecol. India 67, 109–118. doi:10.1007/s13224-016-0933-8

Nakimuli, A., Starling, J.E., Nakubulwa, S., Namagembe, I., Sekikubo, M., Nakabembe, E., Scott, J.G., Mo, A., Aiken, C.E., 2020. Relative impact of pre-eclampsia on birth weight in a low resource setting : A prospective cohort study. Pregnancy Hypertens. 21, 1–6. doi:10.1016/j.preghy.2020.04.002

Nathan, H.L., Paul, T., Greeff, A. De, Conti-, F., Anthony, J., Steyn, W., Hall, D.R., Chappell, L.C., Andrew, H., 2018. Maternal and perinatal adverse outcomes in women with pre-eclampsia cared for at facility-level in South Africa : a prospective cohort study. J. Glob. Health 8, 1–10. doi:10.7189/jogh.08.020401

Nesa, F., Chowdhury, F., Yasmeen, B.H.N., Begum, N., Das, A., 2019. Original Article Serum uric acid level between normotensive and pre-eclamptic patients in third trimester of pregnancy and perinatal outcome. North. Int. Med. Coll. J. 11, 419–422. doi:https://doi.org/10.3329/nimcj.v11i1.50736

Ngwenya, S., 2017. Severe preeclampsia and eclampsia : incidence , complications , and perinatal outcomes at a low-resource setting , Mpilo Central Hospital , Bulawayo, Zimbabwe. Dove Press J. 9, 353–357.

Ngwenya, S., Jones, B., Mwembe, D., 2019. Determinants of adverse maternal and perinatal outcomes in severe preeclampsia and eclampsia in a low‐resource setting , Mpilo Central Hospital , Bulawayo , Zimbabwe. BMC 12, 1–5.

NICE, 2015. Preterm labour and birth overview, National Institute for Health and Care Excellence. London.

Nisar, M.I., Yoshida, S., 2022. Population-based rates, risk factors and consequences of preterm births in South-Asia and sub-Saharan Africa: A multi-country prospective cohort study. J. Glob. Health 12. https://doi.org/10.7189/jogh.12.04011

Obagah, L., Kasia, B.E., Jeremiah, I., Allagoa, D.O., Aigere, E.E.O.S., Kotingo, E.L., Oriji, C.P., 2020. Serum uric acid: a biochemical prognostic indicator of pregnancy outcomes among pre-eclampsia patients at the federal medical centre, Yenagoa. Int. J. Reprod. Contraception, Obstet. Gynecol. 9, 4344.

Pacarada, M., Gashi, A., Beha, A., Obertinca, B., 2016. Case Report of Severe Preeclampsia and Associated Postpartum Complications Case Report. J. Case Reporst Stud. 4, 4–7. doi:10.15744/2348-9820.4.408

Pecoraro, V., Trenti, T., 2020. European Journal of Obstetrics & Gynecology and Reproductive Biology Predictive value of serum uric acid levels for adverse maternal and perinatal outcomes in pregnant women with high blood pressure . A systematic review and meta-analysis. Eur. J. Obstet. Gynecol. 252, 447–454. doi:10.1016/j.ejogrb.2020.07.042

Rewatkar, M., Kedar, K., Tadas, A., 2019. Hyperuricemia : Increase Risk of Maternal & Fetal Complications ( Outcome ) in Preeclampsia. Int. J. Sci. Res. (IJSR), 8, 857–860.

Rotshenker-Olshinka, K., Arnon, S., Gabbay, E., Sela, H.Y., 2016. A Rare Manifestation of a Common Disease : Very Early Severe Preeclampsia in a Low-Risk Patient. Obstet. Gynecol. Int. J. 5, 7–9. doi:10.15406/ogij.2016.05.00185

Ryu, A., Cho, N.J., Kim, Y.S., Lee, E.Y., 2019. Predictive value of serum uric acid levels for adverse perinatal outcomes in preeclampsia. Medicine (Baltimore). 98. doi:org/10.1097/MD.0000000000015462

Saad, N., Beltagy, E., Saad, S., Deen, E., Abbas, M., Emad, R., El, A., 2011. Can serum free fatty acids assessment predict severe preeclampsia ? Alexandria J. Med. 47, 277–281. doi:10.1016/j.ajme.2011.09.003

Saad, O.E., Tanouti, S., Bkiyar, H., Mimouni, A., Housni, B., 2020. Near death 18 weeks preeclampsia in molar pregnancy. Int. J. Reprod. Contraception, Obstet. Gynecol. 9, 877–880. doi:http://dx.doi.org/10.18203/2320-1770.ijrcog20200399

Sacchi, C., Marino, C., Nosarti, C., Vieno, A., Visentin, S., Simonelli, A., 2020. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: A systematic review and meta-analysis. JAMA Pediatr. 174, 772–781. https://doi.org/10.1001/jamapediatrics.2020.1097Shah, A.K., Rajamani, K., Whitty, J.E., 2008. Eclampsia : A neurological perspective 271, 158–167. doi:10.1016/j.jns.2008.04.010

Shazly, S.A., Ahmed, I.A., Radwan, A.A., Abd-elkariem, A.Y., El-dien, N.B., Ragab, E.Y., Abouzeid, M.H., Shams, A.H., Ali, A.K., Hemdan, H.N., Hemdan, M.N., Nassr, A.A., Faten, F., 2020. Middle-East OBGYN Graduate Education ( MOGGE ) Foundation Practice Guidelines : Prelabor rupture of membranes ; Practice guideline No . 01-O-19. Middle East OBGYN 10, 1–17. doi:10.7189/jogh.10.010325

Sibai, B.M., Stella, C.L., 2009. Diagnosis and management of atypical preeclampsia-eclampsia. J. Obstet. Gynecol. 200, 1–8. doi:10.1016/j.ajog.2008.07.048

Singh, A., Sharma, P., Malla, R., Singh, S., 2014. Raised Uric Acid Level and Fetal Outcome in Hypertensive Disorders of Pregnancy. NJOG 9, 78–81.

Sulistyowati, S., 2017. Early and Late Onset Preeclamsia : What did really Matter? Gynecol. Women's Heal. 5, 7–9. doi:10.19080/JGWH.2017.05.555670

Suzuki, T., Ichikawa, D., Nakata, M., Watanabe, S., Han, W., Kohatsu, K., Shirai, S., 2020. Nephrotic syndrome due to preeclampsia before 20 weeks of gestation : a case report. BMC 21, 1–6. doi:https://doi.org/10.1186/s12882-020-01876-9

Tadevosyan, M., Ghazaryan, A., Harutyunyan, A., Petrosyan, V., Atherly, A., Hekimian, K., 2019. Factors contributing to rapidly increasing rates of cesarean section in Armenia: A partially mixed concurrent quantitative-qualitative equal status study. BMC Pregnancy Childbirth 19, 1–10. doi:10.1186/s12884-018-2158-6

Takahashi, M., Makino, S., Oguma, K., Imai, H., Takamizu, A., Koizumi, A., Yoshida, K., 2021. Fetal growth restriction as the initial finding of preeclampsia is a clinical predictor of maternal and neonatal prognoses : a single- center retrospective study. BMC 21, 1–8.

Thangaratinam, S., Sharp, S., Coomarasamy, A., 2006. Accuracy of serum uric acid in predicting complications of pre-eclampsia : a systematic review. BJOG 113, 369–378. doi:10.1111/j.1471-0528.2006.00908.x

UNICEF, World Health Organization, United Nations, World Bank, 2020. A Neglected Tragedy, The global burden of stillbirths.

Ugwuanyi, R.U., Chiege, I.M., Agwu, F.E., Eleje, G.U., Ifediorah, N.M., 2021. Association between Serum Uric Acid Levels and Perinatal Outcome in Women with Preeclampsia. Obstet. Gynecol. Int. 2021. https://doi.org/10.1155/2021/6611828

Uwizeyimana, P., Musabyemariya, E., Tengera, O., Collins, A., 2020. Neonatal Outcomes from Mothers with Hypertension Disorders of Pregnancy: A Retrospective Study at a Referral Hospital in Rwanda. Rwanda J. Med. Heal. Sci. 3, 193–203. https://doi.org/10.4314/rjmhs.v3i2.9

Vega, E.S., 2015. Rising Trends of Cesarean Section Worldwide: A Systematic Review. Obstet. Gynecol. Int. J. 3, 00073. doi:10.15406/ogij.2015.03.00073

Wadhwani, P., Saha, P.K., Kalra, J.K., Gainder, S., Sundaram, V., 2020. A study to compare maternal and perinatal outcome in early vs . late onset preeclampsia. Obstet. Gynecol. Sci. 63, 270–277. doi:https://doi.org/10.5468/ogs.2020.63.3.270

Wagnew, M., Id, M., Chojenta, C., Muluneh, M.D., Loxton, D., 2020. Systematic and meta-analysis of factors associated with preeclampsia and eclampsia in sub-Saharan Africa. PLoS One 15, 1–23. doi:10.1371/journal.pone.0237600

Waters, T.P., Bailit, J.L., 2012. Obstetric and Non-Obstetric Indications for Admission in the Antepartum and Postpartum Periods of Pregnancy. J. Women's Heal. Care 1, 1–6. doi:10.4172/2167-0420.1000104

Weiler, J., Tong, S., Palmer, K.R., 2011. Is fetal growth restriction associated with a more severe maternal phenotype in the setting of early onset pre-eclampsia? a retrospective study. PLoS One 6, 1–5. https://doi.org/10.1371/journal.pone.0026937

WHO, 2004. Low birthweight: country, regional and global estimates.

WHO, 2009. WHO guidelines for the management of postpartum haemorrhage and retained placenta, Human Fertility. Geneva. doi:10.3109/14647273.2010.529650

WHO, 2010. The Global Numbers and Costs of Additionally Needed and Unnecessary Caesarean Sections Performed per Year : Overuse as a Barrier to Universal Coverage, World Health Report. Geneva, Switzerland.

WHO, 2012. Born Too Soon: The Global Action Report on Preterm Birth. Geneva.

Williams, K.P., Galerneau, F., 2002. THE ROLE OF SERUM URIC ACID AS A PROGNOSTIC INDICATOR OF THE SEVERITY OF MATERNAL AND FETAL COMPLICATIONS IN. J. Obstet. Gynaecol. Canada 24, 628–632. doi:10.1016/S1701-2163(16)30193-1

Wolak, T., Shoham-vardi, I., Sergienko, R., Sheiner, E., 2015. High Uric Acid Levels During Pregnancy Linked to Increased Risk for Future Atherosclerotic-Related Hospitalization. J. Clin. Hypertens. 17, 481–485. doi:10.1111/jch.12535

World Health Organization, UNICEF, U.N.P.F. and T.W.B., 2019. TRENDS IN 2000 to 2017 TRENDS IN MATERNAL MORTALITY : 2000 TO 2017. WHO, Geneva.

Wu, Y., Xiong, X., Fraser, W.D., Luo, Z., 2012. Association of Uric Acid With Progression to Preeclampsia and Development of Adverse Conditions in Gestational Hypertensive Pregnancies. Am. J. Hypertens. 25, 711–717. doi:10.1038/ajh.2012.18

Xiong, X., Demianczuk, N.N., Saunders, L.D., Wang, F., Fraser, W.D., 2002. Impact of Preeclampsia and Gestational Hypertension on Birth Weight by Gestational Age. Am. J. Epidemiol. 155, 203–209.

Yakasai, I.A., Gaya, S.A., 2011. Maternal and fetal outcome in patients with eclampsia at Murtala Muhammad specialist Hospital. Ann. Afr. Med. 10, 3–7. doi:10.4103/1596-3519.87049

Yego, F., Este, C.D., Byles, J., Williams, J.S., Nyongesa, P., 2014. Risk factors for maternal mortality in a Tertiary Hospital in Kenya : a case control study. BMC Pregnancy Childbirth 14, 9. doi:10.1186/1471-2393-14-38

You, S., Cheng, P., Chung, T., Kuo, C., Wu, H., Chu, P., 2018. Population-based trends and risk factors of early- and late-onset preeclampsia in. BMC Pregnancy Childbirth 18, 1–11. doi:https://doi.org/10.1186/s12884-018-1845-Maternal

Tam M. Le, Long H. Nguyen, Nam L. Phan, Duong D. Le, Huy V.Q. Nguyen, Vinh Q. Truong, Thanh N. Cao., 2018. Serum uric acid concentration and pregnancy outcomes in women with pre-eclampsia/eclampsia.

# APPENDICES

## Appendix A: Informed Consent

My name is Dr.Lydiah Munialo. I am a qualified medical doctor, registered by the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Master's Degree in Reproductive health at Moi University I would like to recruit you into my research: Association between serum uric acid and maternal and immediate perinatal outcome in preeclamptic women.

**INFROMATION ABOUT PREECLAMPSIA**

Pre- eclampsia (PE) is a multisystem disorder of pregnancy previously defined by the onset of hypertension accompanied by significant proteinuria after 20 weeks of gestation. The incidence and the prevalence of PE are high and cause high mortality and morbidity in developing countries like Kenya. I would like to gather more information about pregnancy outcomes in mothers with PE who have high uric acid and fine out how uric acid affects fetal and maternal outcome.

The information will be useful to health care workers and policy makers in understanding and managing patients in this age group with PE.

**Purpose**: The purpose of this research is the partial fulfillment of the requirements for the Master of Medicine Degree in Reproductive Health and generates information that is going to help in management of preeclamptic women to improve quality of life and reduce mortality and morbidity due to preeclampsia.

**Participants:** If you agree to participate, you will be one of 165 Kenyan pregnant women with Preeclampsia who will be interviewed. Your interviews will be conducted individually to maintain your privacy.

**Procedures:** If you agree to participate, you will be privately asked questions about your medical condition and your medical care during your pregnancy. Our research

team members will write down your responses during the interview, and all of your answers will be kept private. The interview will take between 30 minutes in each phase.

**Benefits & risks:** There is no direct benefit to you for participating in the study. Your choice to not participate will not affect your medical care and your pregnancy. However, your participation, along with that of other pregnant women with PET, will be used to improve future medical services for pregnant women with PET at MTRH.

**Confidentiality:** All of your information will be kept secret, and all discussions with you will be in private. Only the study team will know that you are in the study, and your name will not be shared with anyone. All of your information will be collected under a number assigned to you so that no one other than the study team will know your personal information.

**Cost& payments:** There will be no costs to you for any parts of the study, and you will not receive payment for taking part in this study.

**Contact:** For questions about this study feel free to contact Moi University Institutional Research and Ethics Committee to the following address: Moi Teaching and Referral Hospital Building, 2nd floor, Door no 219, P.O Box 3-30100 Eldoret, Kenya. Office line: 0787723677, Email: irec@mtrh.or.ke, Website: irec.or.ke or investigator: Dr. Lydiah Munialo 0720533431. Email: lydialiambila@gmail.com. Dr. Elkanah Omenge 0722609132 (supervisor) or DR Bett Kipchumba .

By signing this form, you indicate that you have agreed to participate in this research.

Names and signature of participant: _____

Date signed: _____

Signature of witness_____

**Appendix B: Work Plan**

| **Month& year**<br><br>**Activities** | **January to May 2021** | **June to July 2021** | **July to Dec 2021** | **Jan to Dec 2022** | **Jan To May2023** | **May To July 2023** | **July to Sep 2023** | **Sep to Oct 2023** |
|---|---|---|---|---|---|---|---|---|
| Proposal development and approval | | | | | | | | |
| IREC submission and IREC approval | | | | | | | | |
| Training of research assistants | | | | | | | | |
| Data collection and<br>follow up | | | | | | | | |
| Data analysis and thesis writing | | | | | | | | |
| External review | | | | | | | | |
| Dissemination and feedback | | | | | | | | |

**Appendix C: Budget**

| Items | **Quantity** | **Unit Price (Kshs)** | **Total (Kshs)** |
|---|---|---|---|
| ***Stationery & Equipment*** | | | |
| Printing Papers | 8 rims | 500.00 | 4,000.00 |
| Black Cartridges | 3 | 2,000.00 | 6,000.00 |
| Writing Pens | 1 packet | 500.00 | 500.00 |
| Flash Disks | 2 | 2,000.00 | 4,000.00 |
| Box Files | 4 | 200.00 | 800.00 |
| Document Wallets | 4 | 100.00 | 400.00 |
| Internet | 1 | 12000.00 | 12000.00 |
| **Sub total** | | | **27,700.00** |
| *Research Proposal Development* | | | |
| Printing drafts & final proposal | 10 copies | 500.00 | 5,000.00 |
| Photocopies of final proposal | 6 copies | 200.00 | 1200.00 |
| Binding of copies of Proposal | 5 copies | 100.00 | 500.00 |
| **Sub total** | | | **6,700.00** |
| **Lab materials** | | | |
| Cartridges | 10 | 3000 | **30000** |
| Bio analyzer Machine | 2 | 30000 | **60000** |
| **Sub total** | | | **90000** |
| *Personnel* | | | |
| Biostastician | 1 | 30,000.00 | 30,000.00 |
| Research assistants | 4 | 20,000.00 | 80,000.00 |
| **Sub total** | | | **110,000.00** |
| *Thesis Development* | | | |
| Printing of drafts and final thesis | 10 copies | 800.00 | 8,000.00 |
| Photocopy of the final thesis | 6 copies | 200.00 | 1,200.00 |
| Binding of thesis | 6 copies | 300.00 | 1,800.00 |
| *Transport* | | | 10,000.00 |
| **Sub total** | | | **21,000.00** |
| **Total** | | | **165,400.00** |
| **Miscellaneous Expenditure (10% of Total)** | | | **16,540.00** |
| **Grand Total** | | | **271,940.00** |

**Appendix D: Data Collection Tool**

**DEMOGRAPHICS**

1. Patients study number
2. Maternal age (completed years)
3. Weight (in Kgs) ☐
4. Height (meters). ☐
5. Level of education

   a) None ☐ b) Primary ☐ c)Secondary ☐ d) University/college ☐
6. Residence

   a) Urban ☐ b) Rural ☐
7. Marital status (put X or tick)

   a) Single ☐ b) Married ☐ c) Divorced ☐ d) Widowed ☐
8. What is your main occupation?
9. What is your monthly income?

   a).10,000 or less ☐ b).>10,000 ☐
10. Social economic status

    a). Low social economic ☐

    b). Middle social economic ☐

    c). High social economic ☐

**PAST OBSTETRIC HISTORY**

11. Parity ☐
12. Delivered before,

    a) Yes ☐ b) No ☐
13. If delivered before,pre eclampsia in previous pregnancy

    a) Yes ☐ b) No ☐
14. Pregnancy Year of preeclampsia

    1st ☐ 2nd ☐ 3rd ☐ Other ☐

**INDEX PREGNANCY**

15. LMP Day month year ☐
16. Gravida ☐
17. Gestational Age by LMP( in weeks) ☐
18. Gestational Age by U/S ( in weeks) ☐

19. Any family history of PE/ HDP

a) Yes ☐ b).No ☐

20. ANC attended (insert X or tick)

a) Yes ☐ b). No ☐

If NO, go to question 19.

21. ANC attendance (insert X or tick)

a)The present study center ☐ b) Private clinic/hospital ☐ c) Public ☐

22. Gestation at first ANC attendance

a) less than 20weeks ☐ b) 21-28 weeks ☐ c) 29-36 weeks ☐

d) More than 36 weeks ☐

24. How many times did you attend clinic till time of delivery ☐

23. Any of the following noted in ANC

a) High blood pressure (SBP and DBP) ☐

b) Protein in urine ☐ c) Others ☐

24. The blood pressure at admission?

Systolic mmHg ☐ Diastolic mmHg ☐

25. Level of proteinuria noted at admission

a. +1 ☐ b) ++☐ c).+++☐

26. Documented any concurrent medical conditions?

a) None ☐

c) Cardiac disease ☐

d)Thrombophilia ☐

e) Other (specify) ☐

27. Level of uric acid at admission or within 24hours of admission in labor ward

**Intrapartum period**

28. What was the Blood pressure?

a) Systolic b). Diastolic

29. Was induction of labor done?

a) Yes ☐ b) No ☐

30. If yes, what was the indication?

a) Severe PE ☐

b) Term pregnancy ☐

c) Poor maternal condition ☐

d) Others (specify ☐

31. .Mode of delivery

a) SVD ☐

b) Vacuum extraction ☐

c) C/S ☐

32. If C/S was done what was the indication

a) Poor bishop scores ☐

b) Poor progress ☐

c) Abruption placenta ☐

d) Fetal distress ☐

e) Poor maternal condition ☐

f) 0ther (specify) ☐

**MATERNAL OUTCOME**

33. Specify the severity of PE the mother presented with?

a). Mild PE ☐

b). Moderate ☐

c). Severe PE ☐

34. Any complications?

a) Yes ☐ b) No ☐

35. If yes, what were the complications (reference to the file for clinical diagnosis and laboratory tests such as renal function

a) Renal failure ☐

b) Eclampsia ☐

c) Pulmonary edema ☐

d) Cerebral hemorrhage ☐

e) Abruption placenta ☐

f) HELLP syndrome ☐

g) Preterm labor ☐

h) Other (specify)

36. Admission to ICU

a) Yes ☐ b) No ☐

37. If yes, specify reason for admission?

a) Pulmonary edema ☐

b) Cerebral hemorrhage ☐

c) Difficult reversal from anesthesia ☐

d) Other (specify ) ☐

38. Length of stay in ICU (days) ☐

39. If ARF, was dialysis done?

a) Dialysis ☐ b) Conservative ☐

40. Maternal death

a) Yes ☐ b) No ☐

41. If yes, what was the cause of death?

a) ARF ☐

b) Cerebral hemorrhage ☐

c) Pulmonary edema ☐

d) DIC ☐

e) Sepsis ☐

f) Cardiopulmonary failure ☐

g) Other specify ☐

**FETAL OUTCOMES**

42. Newborn outcome

a) Live ☐

b) FSB ☐

c) MSB ☐

d) Neonatal deat ☐

43. Birth weight of baby

a)<2500g ☐ b) >2500g ☐

40. Apgar scores at one minute

41. Apgar scores at five minute

42 Vitals

a) BPs (in mmHg) ☐

b) Pulse rate (bpm) ☐

c) SPO2 (in percentage) ☐

d) Respiratory rate (bpm ☐

e)Temperature ☐

43. Admission at NBU/NICU?

a) Yes ☐ b) No ☐

44. If yes, please specify the reason below:

a) Neonatal sepsis ☐
b) Hypothermia ☐
c) Hypoglycemia ☐
d) Birth Asphyxia ☐
e) Low birth weight ☐
f) Prematurity ☐
g) Other reason (please specify)……

## Appendix E: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2021/63
***Approval Number: 0003911***
24th June, 2021

Dr. Lydiah Nelima Munialo,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
**ELDORET-KENYA.**

Dear Dr. Munialo,

**CORRELATION OF MATERNAL SERUM URIC ACID AND MATERNAL AND PERINATAL OUTCOME IN PREECLAMPTIC WOMEN AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET KENYA**

This is to inform you that ***MTRH/MU-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN: 0003911.*** The approval period is **24th June, *2021- 23rd June, 2022.***
This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, Material Transfer Agreements (MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MTRH/MU-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MTRH/MU-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MTRH/MU-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from ***MOH at the recommendation of NACOSTI*** for each batch of shipment.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MTRH/ MU-IREC.***

Prior to commencing your study; you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and other relevant clearances from study sites including a written approval from the CEO-MTRH which is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH) and its satellites sites.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
24 JUN 2021
APPROVED
P. O. Box 4606-30100 ELDORET

Sincerely,

**PROF. E. WERE**
**CHAIRMAN**
**INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE**

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

## Appendix F: IREC Approval

An ISO 9001:2015 Certified Hospital

# MOI TEACHING AND REFERRAL HOSPITAL

Telephone :( +254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

**Ref:** ELD/MTRH/R&P/10/2/V.2/2010

25th June, 2021

Dr. Lydiah Nelima Munialo
Moi University
School of Medicine
P.O. Box 4606-30100
**ELDORET-KENYA**

**CORRELATION OF MATERNAL SERUM URIC ACID AND MATERNAL AND PERINATAL OUTCOME IN PREECLAMPTIC WOMEN AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA**

You have been authorised to conduct research within the jurisdiction of Moi Teaching and Referral Hospital (MTRH) and its satellites sites. You are required to strictly adhere to the regulations stated below in order to safeguard the safety and well-being of staff, patients and study participants seen at MTRH.

1. The study shall be under Moi Teaching and Referral Hospital regulations.
2. A copy of MTRH/MU-IREC approval shall be a prerequisite to conducting the study.
3. Studies intending to export human bio-specimens must provide a permit from MOH at the recommendation of NACOSTI for each shipment.
4. No data collection will be allowed without an approved consent form(s) to participants unless waiver of written consent has been granted by MTRH/MU-IREC.
5. Take note that **data** collected must be treated with due confidentiality and anonymity.

The continued permission to conduct research shall only be sustained subject to fulfilling all the requirements stated above.

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
25 JUN 2021
SIGN.....
P.O. BOX 3-30100, ELDORET

June 25/06/2021
**DR. WILSON K. ARUASA, *EBS***
**CHIEF EXECUTIVE OFFICER**
**MOI TEACHING AND REFERRAL HOSPITAL**

c.c. - Senior Director, Clinical Services
- Director of Nursing Services
- HOD, HRISM